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(54) Title: IMPROVED DEVICE AND METHOD FOR TREATING CONDITIONS OF A JOINT

(57) Abstract: An implantable drug delivery system is provided including a mechanical member attachable to a portion of a body, a first chamber having an opening configured to receive a sustained release device, a sustained release device, and a removably attachable retainer for retaining the sustained release device in the first chamber. A method for administering a drug to a joint is provided including the steps of positioning a mechanical member in or adjacent a bone, the mechanical member configured to hold a sustained release drug delivery device at a substantially controlled rate. Also provided is a sustained release device intraarticularly implantable into a joint to deliver a therapeutically effective compound within a synovial capsule of the joint such that, in one aspect, the synovial fluid concentration of the compound is greater than the plasma concentration of the compound during the prolonged lifetime of the device, thereby eliminating unwanted systemic side effects and the need for frequent and repeated administrations.

IMPROVED DEVICE AND METHOD FOR TREATING CONDITIONS OF A JOINT

FIELD OF THE INVENTION

The present invention relates to the delivery of therapeutic compounds to joints, particularly to the sustained delivery of anti-inflammatory compounds to joints to treat arthritis.

BACKGROUND OF THE INVENTION

Pain, in and of itself, constitutes a sufficient impetus for remedial action. Moreover, otherwise productive Individuals lose more time due to pains, particularly in the joints, than to any other cause. Civilization and technological advances have ushered in a relatively sedentary existence, both as to work environment and leisure activities, which increases the likelihood of such pain-causing ailments. Although the term is applied to a wide variety of disorders, arthritis generally denotes the inflammation of a joint whether as a result of a disease, an infection, a genetic defect or some other cause. The long term effects of arthritis range from chronic pain to crippling disability.

Osteoarthritis is a disease that attacks cartilage. Surfaces of joint cartilage and underlying bone compress and become irregular, leading to pain, inflammation, bone spurs and limited movement. Osteoarthritis is one of the most common disabilities in the United States, affecting over 15% of the population. As osteoarthritis progresses, serious joint damage and chronic pain can result. Treatment alternatives are limited and, in many cases, ineffective. Aside from weight reduction and avoiding excessive stress on the joint cartilage, there is currently no specific treatment to halt cartilage degeneration or to repair damaged cartilage caused by osteoarthritis. The goal of treatment is to reduce joint pain and inflammation while improving and maintaining joint function. Current pharmacological

treatments include oral anti-inflammatory and anti-pain medications. The effectiveness of these treatments decreases as the disease progresses. In severe osteoarthritis, joint replacement surgery is common. Sometimes surgery is forestalled with injections of steroids into the affected joint, but the delivery of drugs in this manner is painful, and the drugs themselves provide decreasing effectiveness and wear off after several weeks. In 1999, there were over 500,000 joint replacement surgeries funded by Medicare in the United States, which were likely mainly due to osteoarthritis.

Severe arthritis involves a serious auto-immune reaction for which steroids theoretically provide treatment but their efficacy is compromised by the systemic toxicity resulting from the dosage required to penetrate the natural barriers of the joints and the need for repeated treatments due to the chronic nature of the disease.

Steroids may be administered in many different ways. They can be given as tablets, or by injection into a muscle or into a vein.

Steroid injections are a common treatment for a variety of conditions in which inflammation causes pain, swelling and other problems. Joint pain due to osteoarthritis and rheumatoid arthritis are examples of conditions for which steroid injections may be helpful. Injections have the advantage of placing the steroids, often glucocorticoids, for example, directly into a painful area. Because of this, steroid injections are able to reduce inflammation and pain relatively quickly. Unfortunately, steroid injections are a procedure that must be administered by a medical doctor, they are sometimes accompanied by an anesthetic to numb the area to be injected, and the effects of a steroid injection typically last for about only several months before a second injection is required. Furthermore, the injected area may become more painful over the first 24 hours after the local anaesthetic wears off, requiring application of a cold compress or taking painkillers. In addition, it is usually suggested that the joint be rested for 24-48 hours after the injection, especially, for weight

bearing joints such as the knee. Immediately after injection, the concentration of steroid within the joint is maximal. The injection becomes progressively less effective however as the steroid leaches out of the joint. For the above reasons, repeated injections to maintain therapeutic drug concentrations are not clinically acceptable and, consequently, high initial doses are sometimes given. This strategy, however, has the risk of producing toxicity if too much is given at one time.

Common side effects associated with steroid treatment include weight gain, thinning of the bones (osteoporosis), easy bruising, indigestion, mood changes, rises in blood sugar and blood pressure, and increased likelihood of developing infections. Because of their long-term side effects, it is recommended that corticosteroids should be given only after a careful and usually prolonged trial of less hazardous drugs. Furthermore, severe rebound follows the withdrawal of corticosteroids in active diseases, in part due to the down regulation of naturally occurring glucocorticoid steroids.

Intraarticular injections of corticosteroids may temporarily help control local synovitis in one or two particularly painful joints. Triamcinolone hexacetonide may suppress inflammation for the longest time; other depot corticosteroids, including prednisolone tertiary-butylacetate, also are effective. The soluble 21-phosphate preparations of prednisolone or dexamethasone are not recommended because of rapid clearance from the joint and very short duration of action. Side effects may not be as pronounced when steroids are given by injection to the knee. However, the effects of a steroid injection to the knee typically is limited to several months before another injection is required. Also, injections provide an initial level of steroid that is greater than therapeutically required and which rapidly declines beneath therapeutic levels.

Cytotoxic/immunosuppresive compound (e.g., methotrexate, cyclosporine) are increasingly used for severe, active rheumatoid arthritis. They can suppress inflammation

and may allow reduction of corticosteroid doses. Yet, major side effects can occur, including liver disease, pneumonitis, and bone marrow suppression. Thus, patients require careful supervision by a specialist.

Broadly, there exists a need for an improved implantable sustained release drug delivery device and method and apparatus for implantation of said device. In particular, there exists a need for an improved device and method for treating conditions of joint or bones, such as arthritis, without undesirable systemic side effects and a need for repeated injections.

SUMMARY OF THE INVENTION

An advantage of the present invention is a method for treating conditions of the joint without undesirable systemic side effects.

An additional advantage of the present invention is a method for treating conditions of the joint without the need for repeated injections.

An advantage of the present invention is a method for long-term drug treatment without the need for frequent injections of a drug or drugs.

Another advantage of the present invention is a sustained release, implantable drug delivery device that is useful for treating medical conditions, such as but not limited to inflammatory or degenerative conditions.

Additional advantages and other features of the invention will be set forth in the description which follows and in part will become apparent to those having ordinary skill in the art upon examination of the following or may be learned from the practice of the invention. The advantages of the invention may be realized and obtained as particularly pointed out in the appended claims.

According to the present invention, the foregoing and other advantages are achieved, in part, by a method for locally administering a therapeutically effective compound to a joint

of a mammal that comprises the step of: intraarticularly implanting a sustained release device to deliver the therapeutically effective compound within a synovial capsule of the joint, such that synovial fluid concentration of the compound is greater than plasma concentration of the compound.

In accord with aspects of the present invention, the foregoing and other advantages are also achieved in part by an implantable sustained release device for locally administering a therapeutically effective compound to a joint. The device contains a therapeutically effective compound and is configured to provide sustained release of the compound to synovial fluid such that the synovial fluid concentration remains greater than plasma concentration.

In another aspect of an implantable sustained release drug delivery device in accord with the invention, there is provided a mechanical member attachable to a portion of a body, a first chamber having an opening configured to receive a sustained release device, and a removably attachable retainer for retaining the sustained release device in the first chamber.

In still another aspect of an implantable sustained release drug delivery device in accord with the invention, there is provided a system comprising a mechanical member attachable to a portion of a body, a chamber disposed within the mechanical member configured to receive a sustained release device bearing at least one drug, and an opening in the chamber to permit release of the at least one drug borne by the sustained release device.

Another aspect of the present invention provides a method for administering a drug to a joint, the method comprising the step positioning a drug delivery system in a bone, the system configured to hold a sustained release drug delivery device.

Yet another aspect of the present invention provides a method for administering a drug to a joint, the method comprising the steps of positioning a mechanical member in or adjacent a bone, said mechanical member configured to hold a sustained release drug delivery

device bearing at least one drug, and outputting said at least one drug from said sustained release drug delivery device at a substantially controlled rate.

Still another aspect of the invention is envisaged in an implantable sustained release device for locally administering a drug, comprising a bone screw including a hollow portion configured to receive a sustained release holding device, the sustained release holding device itself configured to receive a drug payload. In an aspect thereof, a drug payload including one or more drugs is included, as is a rate-limiting barrier configured to limit a release rate of a drug from the drug payload to thereby provide sustained release of the drug. The rate-limiting barrier may itself be configured to provide a steady-state release rate of a drug from the drug payload substantially equal to a steady-state rate of elimination of the drug from a treatment site and to provide a predetermined therapeutic concentration of the drug in the treatment site, said predetermined therapeutic concentration of the drug being greater than a plasma concentration of the drug until substantially all of the drug in the drug payload is depleted.

Additional advantages of the invention will become readily apparent to those skilled in the art from the following detailed description, wherein various embodiments of the invention are described simply by way of illustrating of the best mode contemplated in carrying out the invention. As will be realized, the invention is capable other and different embodiments, and its details are capable of modifications in various obvious respects, all without departing from the invention. For example, the aspects of the invention presented herein are similarly applicable to other medical applications, including but not limited to bone fixation and localized treatments adjacent bone masses. Accordingly, the description is to be regarded as illustrative and not as restrictive.

BRIEF DESCRIPTION OF THE DRAWINGS

By way of example only, embodiments of the present invention will be described with reference to the accompanying drawings, in which:

FIG. 1 shows a graph of fluocinolone acetonide (FA) in plasma versus synovial fluid in sheep in accord to one aspect of the invention.

FIGS. 2A and 2B respectively show an exploded cross-sectional view of a drug delivery system according to an embodiment of the present invention and a top view of a removable attachable retainer according to an embodiment of the present invention.

FIG. 3 shows an exploded cross-sectional view of a drug delivery system according to a further embodiment of the present invention.

FIG. 4 shows a top view of a removable attachable retainer according to the embodiment of the present invention shown in Fig. 3.

FIG. 5 shows an exploded cross-sectional view of a drug delivery system according to a further embodiment of the present invention.

FIG. 6 shows a cross-sectional view of a drug delivery system according to a further embodiment of the present invention.

FIG. 7 shows a cross-sectional view of a drug delivery system according to a further embodiment of the present invention.

FIG. 8 shows a cross-sectional view of a drug delivery system according to yet another embodiment of the present invention.

FIGS. 9A-9C depict top views of the drug delivery system depicted in FIG. 8.

FIGS. 10A-10C depict cross-sectional views of a drug delivery system according to an embodiment of the present invention.

FIGS. 11A-11B depict cross-sectional views of another drug delivery system according to an embodiment of the present invention.

FIGS. 12A-12F depict cross-sectional views of a drug delivery system according to another embodiment of the present invention.

FIGS. 13A-13B depict cross-sectional views of an aspect of a drug delivery system according to another embodiment of the present invention.

FIGS. 14A-14D illustrate various cross-sectional views of aspects of a drug delivery system according to the embodiments of the present invention represented in Figures 12A-12D and/or 13A-13B.

FIGS. 15A-15B illustrate an apparatus used to insert a drug delivery device in accord with the invention.

FIGS. 16A-16G illustrate a method of inserting a drug delivery device in accord with the invention.

DESCRIPTION OF THE INVENTION

The present invention provides a method for administering a therapeutically effective compound to the synovial fluid of a joint. The method comprises the step of implanting a sustained release device within the joint such that the therapeutically effective compound is released within the synovial capsule. The synovial fluid concentration of the compound remains greater than plasma concentration for the lifetime of the sustained release device. In one aspect of the invention, the synovial fluid concentration of the compound remains at least one order of magnitude greater than the plasma concentration. In a preferred aspect of the invention, the synovial fluid concentration of the compound remains several orders of magnitude greater than the plasma concentration.

The present invention is particularly effective in treating joint diseases, such as inflammatory joint diseases, e.g., various forms of arthritis. Examples of inflammatory joint diseases which can be effectively treated in accordance with embodiments of the present invention include arthritis associated with spondylitis, diffuse connective tissue diseases such as rheumatoid arthritis, infectious arthritis and osteoarthritis.

Various therapeutically effective compounds can be effectively employed in implementing embodiments of the present invention include, for example, glucocorticoids, anti-inflammatories such as dexamethasone, fluocinolone, cortisone, prednisolone, flumetholone, and derivatives thereof; as well as, non-steroidal anti-inflammatory drugs and cyclosporines.

As employed throughout this disclosure, the expression, "sustained release device" is intended to mean a device that is capable of releasing a drug(s) or compound over an extended period of time in a controlled fashion. The drug(s) or compound may advantageously include, but are not limited to, a steroid, an anti-inflammatory drug, antibiotic, anti-viral agent, cancer-fighting drug, or a pain reliving drug. Examples of

sustained release devices useful in the present invention may be found in, for example, U.S. Patent Nos. 6,051,576, 5,773,019, 6,001,386, 5,902,598, and 5,378,475 (incorporated herein by reference, in their entireties). Suitable sustained release devices could comprise an inner core bearing an effective amount of at least one low solubility agent and at least one non-bioerodible polymer coating layer which is permeable to low solubility agent(s). Suitable low solubility agents may include and are not limited to corticosteroids such as dexamethasone and triamcinolone acetonide, angiostatic steroids such as trihydroxy steroid, antibiotics including ciprofloxacin, and non-steroidal anti-inflammatory agents such as indomethacin and flurbiprofen, co-drugs including low solubility co-drugs of salts or conjugates of synergistic pharmacological agents such as suramin/amiloride or 5-FU/THS, and combinations thereof. Standard pharmaceutical textbooks provide procedures to obtain a low solubility form of a drug. By "low solubility", it is meant a solubility less than about 10μg of compound per 1 ml (of water at a temperature of 25°C as measured by procedures set forth in the 1995 USP). This includes compounds which are slightly soluble (about 0.01 μg/ml-about 0.001 μg/ml), very slightly insoluble (about 0.001μg/ml-about 0.0001 μg/ml) and practically insoluble or insoluble compounds (less than about 0.0001 μg/ml).

Embodiments of the present invention include the sustained release of two or more drugs simultaneously. The sustained release device is configured, in one aspect of the invention, to provide release of a compound to synovial fluid such that the synovial fluid concentration remains greater than plasma concentration. The sustained release device is designed to maintain an optimal dosage level at the target site over the entire duration of treatment without substantial variability in dosing over time.

The sustained release device may be surgically implanted intraarticularly, i.e., within the synovial joint. In embodiments of the present invention, the sustained release device may be configured for attachment to a bone, as in co-pending U.S. Provisional Patent Application

Serial Nos. 60/245,184 and 60/291,606, the entire disclosures of which are incorporated by reference herein. In other embodiments, the sustained release device may be configured for attachment to a ligament with suturing.

The concentration of the compound in the synovial fluid remains greater than the plasma concentration of the compound during the lifetime of the device. As the compound is released from the device, it enters the synovial fluid. Over time a steady state condition is established where the rate of compound entering the synovial fluid is substantially equivalent to the rate of compound eliminated from the joint. The compound that is eliminated from the joint is then distributed throughout the rest of the body and is eliminated via excretion. This redistribution and excretion establishes the differential levels between the synovial fluid and the plasma. In embodiments of the present invention, the plasma concentration of the compound remains at or below 5 ng/mL. At such low concentrations, adverse systemic side effects are unlikely to develop. In contrast, the synovial fluid concentrations remain substantially therapeutic, during release of the compound from the sustained release device. The exact concentration depends on the condition and therapeutic index of the compound.

The present invention provides sustained release of the therapeutically effective compound for a duration of about 3 months to about 10 years, such as from about 6 months to about 5 years. In embodiments of the present invention, sustained release of the therapeutically effective compound is provided for about 3 years. As such, the need for frequent, repeated administrations, such as with injections is avoided.

The following examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become more apparent to those skilled in the art in light of the present disclosure.

TWELVE MONTH SINGLE DOSE TOXICITY STUDY IN BEAGLE DOGS

ANIMALS

Species: *Canis familiaris*
Strain: Beagle
Source: Covance
Age at Initiation: 5-9 months
Weight at Initiation: 10 - 12 kg, to be documented in the study file
Number of Males (including spares): 6 + 1 spare

EXPERIMENTAL METHODOLOGY

STUDY DESIGN

Group Number	Number of Animals Males	Device	Dosing Regimen	Euthanasia
1	3	Fluocinolone acetonide implant	1 implant in each hindlimb joint	1/group at Day 29, 91, and 365
2	3	Fluocinolone acetonide implant	4 implants in each hindlimb joint	

FREQUENCY AND DURATION OF ADMINISTRATION

Devices were administered once via bilateral intraarticular implants. The day of surgical implantation was Day 1.

IMPLANTS

The devices were made as follows. Fluocinolone acetonide, USP, was compressed into 1.5mm diameter tablets using standard pharmaceutical methods. The tablets were placed into preformed cups made from silicone elastomer. Cup size was dependent on dosage form. These cups were attached to polyvinyl acetate (PVA) suture tabs. For the 2 mg implants, the surface of the tablet not coated with silicone was attached to a suture tab with PVA solution. For the 6 mg implant, a side of the silicone cup was attached perpendicular to the suture tab. Finally, the assemblies are dip coated with PVA.

The implants were then cured at 135°C for 5 hours and placed within the primary package. The product in the primary package was placed in a self-adhesive pouch and sterilized using gamma irradiation.

PREOPERATIVE PROCEDURES

ANESTHESIA AND ANTIBIOTIC THERAPY

The animals were preanesthetized with atropine (0.4 mg/kg IM) and acepromazine (0.1 mg/kg IM). After about 10-30 minutes, the animals were initially anesthetized with methohexital INa at 10-15 mg/kg IV, to effect. The animals were immediately intubated and maintained in anesthesia with isoflurane inhalant anesthetic delivered through a volume regulated respirator. The $ETCO_2$ was maintained within individual physiological ranges. An intravenous drip of lactated Ringer's solution was begun at a rate of approximately 10 mL/kg/hr. Procaine/Benzathine penicillin (40,000 IU/kg, IM) was also given.

SURGICAL PREPARATION

Hair was removed from the entire leg. Any excess hair was removed by vacuum. The surgical site was prepared for aseptic surgery by first washing the leg with povidone-iodine scrub solution followed by an application of 70% isopropyl alcohol, which was allowed to dry. Dura-Prep™ or similar solution was then applied to the entire leg and also allowed to dry. The entire leg, including the foot, was appropriately draped for strict aseptic surgery.

SURGICAL PROCEDURES

Surgery was performed on both knee joints of all animals. A lateral skin incision was made to expose the fascia lata overlying the vastus lateralis cranially and the biceps femoris caudally. The joint was exposed through an incision in the lateral intermuscular septum to expose the femur by anterior retraction of the vastus lateralis and posterior retraction of the biceps femoris. Care was taken not to disrupt the tendon of origin of the long digital extensor as it originates from the lateral femoral condyle. The joint capsule was opened, the patella luxated medially, and the joint was held in full flexion. 2mg devices were placed in the right

leg and 18 mg implants were placed in the left leg. The implants were placed within the anterior intercondyloid fossa, immediately lateral to the origin of the posterior cruciate ligament. The bone may be slightly deepened at this location with a curette to accept the implant. The implant was sutured in place to the posterior cruciate ligament. The joint capsule was closed with 3/0 PDS in a simple interrupted fashion. The retinaculum and intermuscular septum were closed with 2/0 Vicryl in a continuous pattern. The fascia lata were closed with 2/0 PDS, and the subcutaneous tissues with 3/0 PDS, both in a simple continuous pattern. The skin was closed with 3/0 Vicryl in a subcuticular pattern.

BLOOD COLLECTION

Blood was collected from a peripheral vessel. Blood volumes represent whole blood and are approximate amounts.

Timepoint	Clinical Pathology				BAC	
	Hematology	Clinical Chemistry	Coagulation	Cortisol	Blood	Synovial Fluid
Days 3, 7, 21, 29, 91, and 365	X	X	X	X	X	X
Volume of Whole Blood/Timepoint	1.3 mL	1.8 mL	1.8 mL	1.8 mL	5.0 mL	0.3-0.5mL
Anticoagulant	EDTA	None	Sodium Citrate	None	EDTA	EDTA

The blood samples were processed for plasma, the plasma was extracted, and the plasma will be placed immediately in a ≤-70°C freezer until transferred for analysis.

SYNOVIAL FLUID

After anesthesia (acepromazine, 0.2 mg/kg, IM followed by sodium pentobarbital, 22 mg/kg, IV, to effect) an attempt was made to obtain synovial fluid. Synovial fluid samples were immediately stored at ≤-70°C in polypropylene tubes until transferred.

TABLE 1

Assayed Concentrations (ng/mL) of Fluocinolone Acetonide in Dog Plasma Samples

Time (Days)	Dog 1001	Dog 1002	Dog 2001	Dog 2002	Dog 3001	Dog 3002
3	1.89	BQL	BQL	BQL	BQL	BQL
7	BQL	BQL	BQL	BQL	16.9	BQL
21	0.57	BQL	BQL	BQL	4.92	BQL
29	BQL	BQL	BQL	BQL	BQL	BQL

BQL = Below Quantition Limit, 0.5 ng/mL

TABLE 2

Assayed Concentrations (ng/mL) of Fluocinolone Acetonide in Dog Synovial Fluid Samples (Left Leg)

Time (Days)	Dog 1001	Dog 1002	Dog 2001	Dog 2002	Dog 3001	Dog 3002
3	656	357	89.0	193	788	207
7	290	405	194	279	35300	251
21	1070	373	X	393	5180	276
29	457	379	57.8	956	X	210
56	202071	541	X	X	36.9	X

BQL = Below Quantition Limit, 5 ng/mL

X = No sample collected for this timepoint

TABLE 3

Assayed Concentrations (ng/mL) of Fluocinolone Acetonide in Dog Synovial Fluid Samples (Right Leg)

Time (Days)	Dog 1001	Dog 1002	Dog 2001	Dog 2002	Dog 3001	Dog 3002
3	52.0	36.6	600	24.4	57.9	40.7
7	62.4	BQL	98.4	47.7	171	8.30
21	7.27	BQL	BQL	144	51.5	BQL
29	BQL	BQL	BQL	BQL	16.4	7.86
56	19.3	BQL	X	X	X	BQL

BQL = Below Quantition Limit, 5 ng/mL
X = No sample collected for this timepoint

The results shown in Tables 1-3 demonstrate the effectiveness of the present invention.

PHAMACOKINETIC STUDY OF A FLUOCINOLONE ACETONIDE IMPLANT IN THE STIFLE JOINT OF SHEEP

ANIMALS

Species:	*Ovis aries* (Sheep)
Strain:	Rambouillet
Source:	K Bar Livestock
Age at Initiation:	Adult
Weight at time of surgery/treatment:	35-75 kg.
Number and Sex:	12 males +1 spare
	12 females (nonpregnant) + 1 spare

EXPERIMENTAL METHODOLOGY

The objective of this study was to determine both the local and systemic pharmacokinetic profile of an intra-articular fluocinolone acetonide (FA screw) implant in the stifle joint of sheep. This study group consisted of 24 animals randomized into 2 groups of 6 males and 6 females per group, as shown in Table 4. The animals underwent surgical implantation of the FA Screw test device in the stifle joint on Day 1. Following a recovery period, blood and synovial fluid were collected periodically for pharmacokinetic determination. Following completion of a 24 month observation period, the animals will be euthanized and subjected to necropsy.

Study Design - TABLE 4

Group Number	Number of Animals		Test Device	Dosage Level*	Dosing Regimen	Euthanasia/ Necropsy Day
	Males	Females				
1	6	6	FA Screw	1 implant	Surgical implantation of test device in one stifle joint	24 months after implantation
2	6	6		3 implants		

*Each implant nominally delivers approximately 60 micrograms/day of fluocinolone acetonide

FREQUENCY AND DURATION OF ADMINISTRATION

Devices were administered once via surgical implantation on Day 1.

IMPLANTS

The implant is a polymer-coated, sustained-release delivery system for Fluocinolone Acetonide (FA). The implant contains 55 mg of FA and is designed to deliver the drug for approximately 3 years. The tablet core contains approximately 55 mg of FA granulated with 10 % PVA. The tablet core is positioned and adhered via an adhesive, such as a silicone adhesive, in the interchangeable head of the bone screw. The overall device geometry is that of a cancellous bone screw (i.e. the base) in which the head of the screw has been hollowed out to accept a removable cup (i.e. the payload) containing the drug tablet. In this embodiment, the screw is approximately 11/16" in length and is no more than ¼" at its widest point (i.e. the screw head). The payload is sized to fit into the screw and to accommodate the tablet.

PREOPERATIVE PROCEDURES

ANESTHESIA AND ANTIBIOTIC THERAPY

ProBios® or the equivalent (15 grams per os) was administered prior to surgery and on Day 2. The animals were premedicated with glycopyrrolate (0.02 mg/kg, intramuscularly [IM], butorphanol (0.05 mg/kg, intravenously [IV]), and diazepam (0.2 mg/kg IV). Intravenous indwelling catheters were placed in peripheral veins as needed. Anesthesia was induced with methohexital (~10 mg/kg, IV). The animal was intubated and maintained in anesthesia with Halothane® inhalant anesthetic delivered through a volume regulated respirator, started as soon as possible after intubation. An esophageal tube was also be placed into the rumen to aid in keeping it decompressed. Lactated Ringer's solution was administered intravenously at a rate of ~10 mL/kg/hour. The total volume of crystalloid fluids administered did not exceed 2 L. Antibiotic prophylaxis began prior to surgery with the use of Cefotaxime (50 mg/kg, IV or IM).

SURGICAL PREPARATION

Eye ointment was applied to the eyes and all fleece was clipped from the entire leg, with any excess fleece removed by vacuum. The animal was positioned in lateral recumbency and the surgical site prepared for aseptic surgery by first washing the area with povidone-iodine scrub solution and 70% isopropyl alcohol, which was allowed to dry. Then, Dura-Prep™ or a similar solution was applied to the area and also allowed to dry. The area was then appropriately draped for strict aseptic surgery.

SURGICAL PROCEDURES

A lateral skin incision was made to expose the fascia lata overlying the vastus lateralis cranially and the biceps femoris caudally. The joint was exposed through an incision in the lateral intermuscular septum to expose the femur by anterior retraction of the vastus lateralis and posterior retraction of the biceps femoris. Care was taken not to disrupt the tendon of origin of the long digital extensor as it originates from the lateral femoral condyle. The lateral geniculate vessels may be cauterized during this procedure. The joint capsule was opened, the patella luxated medially, and the joint held in full flexion. The appropriate number of implants (1 for Group 1; 3 for Group 2) were placed either within the anterior intercondyloid fossa (immediately lateral to the origin of the posterior cruciate ligament), the suprapatellar fossa, or the medial femoral condyle. The joint capsule was closed with 2/0 PDS in a simple interrupted fashion. The retinaculum, intermuscular septum, and fascia lata were closed with #2 PDS or Prolene® in a continuous pattern. The subcutaneous tissues were closed with 2/0 PDS and the skin closed with staples.

BLOOD COLLECTION

Blood was collected from a peripheral vessel. Blood volumes represent whole blood and are approximate amounts.

Sample Collection Schedule

Timepoint	Clinical Pathology		Bioanalytical Chemistry	
	Hematology	Serum Chemistry	Blood	Synovial Fluid
Prior to surgery	X	X		
On Day 7			X	X
Once monthly for Months 1-12			X	X
Once quarterly for Months 13-24			X	X
Prior to necropsy	X	X	X	X
Volume of Whole Blood/ Timepoint	0.5 mL	1.8 mL	5.0 mL	0.3 - 0.5 mL
Anticoagulant	EDTA	None	EDTA	EDTA

The bioanalytical chemistry (BAC) blood samples were processed for plasma, the plasma was extracted and stored at ≤-70°C until transferred for analysis.

SYNOVIAL FLUID

After anesthesia, an attempt was made to obtain synovial fluid. Synovial fluid samples were stored at ≤-70°C until transferred. Anesthesia for synovial fluid collection began after a minimum 12 hour fast (maximum 24 hours). An IM injection of diazepam (0.5 mg/kg) was given and then an IV catheter placed, followed by IV injections of 0.035 mg/kg xylazine and 3.0 mg/kg ketamine (combined in a syringe and injected slowly). Additional ketamine may be given as needed in increments of approximately 1 mg/kg. Anesthesia may be reversed with IV injections of yohimbine (0.125 mg/kg) or atipamezole (10 μg/kg).

Figure 1 depicts the measured plasma versus synovial fluid concentrations in sheep and illustrates both the local and systemic pharmacokinetic profiles of intra-articular fluocinolone acetonide implants in the stifle joint of sheep. Figure 1 represents a three-fold

increase in FA concentrations in the synovial fluid of sheep at three and eight weeks. Plasma levels are between 0-0.35 ng/ml reflecting that drug delivered within the joint capsule is maintained at a high level over long periods of time. This differential in plasma and synovial fluid demonstrate the value of local therapy in treating joint disease. These results are illustrative of the general efficacy of the method and apparatus of the invention, but are not to be construed as limiting the scope of the invention in any way.

In an aspect of the invention, the fluocinolone acetonide, USP, are compressed into tablets using standard pharmaceutical methods and are dip coated with PVA, as discussed above, although other conventional processing means for applying the PVA (or other type of polymer coating or rate-limiting diffusion membrane) are acceptable in accord with the invention. Instead of placing the tablets into preformed silicone elastomer cups, however, the tablets are disposed within a bone screw 10 or other type of implantable device, as illustrated for example, in **Figure 2A** and other figures appended hereto, which are described in greater detail below.

A drug delivery system 10 according to one aspect of the present invention is depicted in **Figs. 2A and 2B.** The drug delivery system 10 (hereinafter "system 10") is generally in the form of a hollow-headed screw for attaching a sustained release device to a bone. System 10 comprises a hollow head 11, a neck 12, and a threaded shank 13 for threading system 10 into a hole in a bone. Head 11 is configured to allow system 10 to be screwed into a bone with head 11 substantially flush with the bone; for example, it can be chamfered and include slots S as shown in **Fig. 2B** to accommodate a (wrench). Device 10 is made of a material suitable for long-term insertion in the body, such as conventional surgical stainless steel. System 10 further comprises a chamber 14, such as a cylindrical chamber, formed inside head 11, for holding a sustained release device 15.

Sustained release device 15 includes an inner core 15a comprising an effective amount of a low solubility agent and a non-bioerodible polymer coating layer 15b that is permeable to the low solubility agent, wherein polymer coating layer 15b covers inner core 15a and is essentially non-release rate limiting. The polymer coating layer preferably covers the inner core and is essentially non-release rate limiting. In another aspect, the inner core may be substantially covered by the non-bioerodible polymer coating layer 15b that is not permeable to the low solubility agent, but instead defines and provides a plurality of small openings therein to permit sustained interaction between the inner core 15a and an external environment.

In still another aspect of the invention, the sustained release device 15 may be formed from a bioerodible material bearing a drug or a plurality of drugs. Bioerodible, as used herein, includes bioresorbable and bioabsorbable materials, as well as strictly bioerodible materials. Technically, bioabsorbable or bioresorbable materials are completely metabolized and eliminated from the body, whereas bioerodible materials are not necessary completely broken down and eliminated. Suitable bioerodible (and/or resorbable) polymeric materials include linear aliphatic polyesters (poly-glycolide, lactide, caprolactone, hydroxybutyrate) and their copolymers (poly-[glycolide-lactide], [glycolide-caprolactone], [glycolide-trimethylene carbonate], [lactic acid-lysine], [lactide-urethane], [ester-amide]), polyanhydrides, poly(orthoesters), polyphosphazenes, orthoesters, and poly(orthoester)/poly(ethylene glycol) block copolymers, to name a few. The bioerodible material may comprise combinations of materials or layers to achieve a desired result of bioeroding or bioabsorbing at a known, controlled rate.

Referring to **Figs. 2A and 2B**, system 10 further comprises a removably attachable retainer 16, as of stainless steel, for retaining sustained release device 15 in chamber 14. Retainer 16 is generally cylindrical and comprises threads 17a in its outer wall for threadingly

engaging threads 17b in an inner wall of chamber 14. Retainer 16 further comprises holes 18 for mating with torque transmitting pins of a screwdriver to remove and attach retainer 16 to system 10, and one or more openings 19 for allowing the drug from inner core 15a of sustained release device 15 to escape system 10. Those skilled in the art will understand that retainer 16 can be removably attached to system 10 by methods other than threads 17a, 17b.

In another embodiment of the present invention, shown in **Fig. 5**, a system 50 identical to that shown in **Figs. 2A and 2B** is provided, except that an inner surface 14a of chamber 14 has threads 51a, and a second chamber 52 is removably attachable inside chamber 14. Second chamber 52 carries a sustained release device 53 comprising an inner core 53a and a polymer coating layer 53b, functionally similar to sustained release device 15 described in detail above. Second chamber 52 has threads 51b that threadingly engage threads 51a in the inner wall of chamber 14 to attach second chamber 52 to first chamber 14, and a pair of slots 54 for engaging a tool, such as a screwdriver, to screw second chamber 52 in and out of first chamber 14. After second chamber 52 is attached to chamber 14, retainer 16 is installed as described above.

In another embodiment of the present invention, shown in Fig. 3, system 30 comprises a hollow head 31, neck 32, threaded shank 33 for threading system 30 into a hole in a bone, and a first chamber 34 in head 31, similar to system 10 described above. However, in this embodiment of the present invention, a second chamber 35 is removably attachable inside first chamber 34, and carries a sustained release device 36 comprising an inner core 36a and a polymer coating layer 36b, functionally similar to sustained release device 15 described in detail above. Second chamber 35 has threads 37a that threadedly engage threads 37b in the inner wall of first chamber 34 to attach second chamber 35 to first chamber 34, and a pair of slots 38 for engaging a tool, such as a screwdriver, to screw second chamber 35 in and out of first chamber 34.

Referring now to **Figs. 3 and 4**, system 30 further comprises a removably attachable retainer 39, as of stainless steel, for retaining sustained release device 36 in second chamber 35. Retainer 39 is generally cylindrical and comprises threads 40a in its outer wall for threadingly engaging threads 40b in an inner wall of second chamber 35. Retainer 39 further comprises holes 41 for mating with a screwdriver to remove and attach it to second chamber 35, and one or more openings 42 for allowing the drug from inner core 36a of sustained release device 36 to escape system 30. Those skilled in the art will understand that retainer 39 can be removably attached to second chamber 35 by methods other than threads 40a, 40b.

To attach the system of the embodiments of the present invention shown in **Figs. 2A-5** to a body, such as a human body, a hole, such as but not limited to a chamfered hole, may be first drilled into a bone. The assembled system 10, 30, 50 is then screwed into the hole such that the head of the device is flush with the bone. The sustained release device 15 or second chamber 35, 52 containing the sustained release device can be easily replaced as necessary when the drug of the inner core 15a, 36a, 53a has been completely released without removing the entire system from the body.

In other embodiments of the present invention, illustrated in **Figs. 6 and 7**, the system 60, 70 comprises a staple 61 or a nail 71 that is driven into the bone instead of a screw. Still further, the system 60 illustrated in Figure 6 may be configured to clasp around a body part, such as a bone, by deformation of the outwardly protruding portions of staple 61 until a suitable securement of the staple 61 to the body part is obtained. A chamber 62, 72 holds a sustained release device 63, 73, which is retained in chamber 62, 72 by a removably attachable retainer 64, 74 having a hole 65, 75 for allowing release of the drug. Of course, in the embodiments of **Figs. 6 and 7**, the system 60, 70 does not sit flush with the bone, but protrudes somewhat. To minimize irritation to surrounding soft tissue, the sharply angled edges may be chamfered or rounded.

In still another embodiment of the invention, as shown in **Fig. 8**, a groove 80 is provided in a head 81 of system 85. As depicted, the system comprises a head 81 having a chamber 82, a neck 83, and a threaded shank 84 for threading device 85 into a bone or into a hole formed in a bone. Groove 80 is formed within the head 81 to have an outer diameter D_2 greater than the diameter D_1 of the chamber and is set apart from the top surface of the head 81 so as to be bounded by a retaining ledge 86 on an upper portion thereof. A retaining member 88 is removably insertable within groove 80, as shown in **Figs. 9A-9C**. **Fig. 9A** shows another aspect of the relation between groove 80 and chamber 82. In this embodiment, it is preferred that the retaining member 88 possess a curvilinear shape, such as a c-shape, as shown in **Fig. 9A**, wherein at least a portion of the member has a diameter substantially equal to D_2 and at least a portion having an inner diameter less than D_1. Further, it is desired that this retaining member 88 be at least sufficiently resilient to permit elastic deformation of at least a portion thereof to permit insertion of the retaining member into groove 80.

In an equilibrium state, shown in **Fig. 9C**, the curvilinear member could not be inserted into the groove as it would be blocked by the retaining ledge 86 disposed on an upper side of the groove, retaining ledge possessing a diameter substantially similar to that of chamber 82. By appropriately disposed tensile or compressive forces, however, curvilinear member 88 may be sufficiently elastically deformed from the equilibrium position, depicted by dashed lines in Fig. 9A, to permit insertion into groove 80. In the inserted position, the retaining member 88 resumes its equilibrium position and an outer edge thereof abuts or conforms to the groove outer diameter. Moreover, at least a portion of an inner diameter of the retaining member possesses a diameter less than the diameter D_1 of the chamber 82, thus at least partially occluding the opening to the chamber. In this way, an object in the chamber, such as a sustained release device 53, may be retained within the chamber 82 by the portion

of the retaining member 88 at least partially occluding the chamber. This occluding portion may comprise, as shown in **Fig. 9C**, a curvilinear portion which bounds an inner diameter D_1 of the chamber along an arc substantially equal to a length of the retaining member 88 or may simply comprise one or more projecting portions. Additionally, the degree of occlusion, or blocking of the chamber opening, may be varied in accord with the application by corresponding variation of the inner diameter of the occluding portion or projection portions of the retaining ring 88.

Still another embodiment of the invention is shown in **Figs. 10A-10C**. **Fig. 10A** depicts a top view and a cross-sectional view of a screw 95 having a screw head defining a hollow head 96 therein. A sustained release holding device 100 (**see Fig. 10C**) is detachably insertable into the hollow-head 96 portion of screw 95 to retain and locally deliver a drug provided therein. Screw 95 includes a threaded shank 91 for threading the screw comprising the drug delivery system into a hole in a bone (not shown). It is generally preferred to position a top surface of the screw 95 substantially flush with the bone, by means of an appropriate screw configuration or by provision of appropriate burr holes. In this embodiment, an inside diameter of the hollow head 96 is 0.244 inches and an outer diameter of the hollow head is 0.264 inches. A lip 94 formed at a top portion of the hollow head 96 has an outer diameter of 0.295 inches.

The depth of the hollow head 96 is 0.154 inches and a plurality of torque transmitting structures 97 are provided in a base portion 93 of the hollow head to facilitate mechanical securement of the screw into a receiving surface, such as a bone. These torque transmitting structures 97, as illustrated in **Fig. 10A**, comprise three Phillips-head receiving portions disposed along a diameter of about 0.172 inches to a depth of less than about 0.025 inches. A diameter of the torque transmitting structures 97 may be about 0.048 inches. In accord with previous aspects of the invention, this torque transmitting structure may comprise one or

more slots or may comprise other structures conventionally employed to transmit torques. The threaded shank 91 is at least 0.32 inches in length and possesses, in the illustrated embodiment, a thread 92 having a pitch of 0.69 inches, a root (or minor) diameter of 0.125 inches, and a major diameter of 0.177 inches, wherein the sides of the threads intersect one another at a 30 angle. A tip of the threaded shank 91 is angled, such as at a 30 angle to facilitate insertion.

Formed within an upper portion of the threaded shank 91 exposed to the hollow head 96 is a recessed threaded portion 98 having a depth of about 0.18 inches. As shown in Fig. 10A, the minimum thread depth is approximately 0.110 inches with a thread major diameter of about 0.0595 inches. **Fig. 10C** illustrates the corresponding threaded shank 99 of the sustained release holding device 100. The sustained release holding device 100 is configured for insertion into the hollow head 96 of screw 95. As such, the outer diameter of the sustained release holding device 100 is 0.236 inches and the depth is approximately 0.170 inches. The inner diameter of the sustained release holding device 100 is 0.183 inches. At an upper portion thereof is a lip 102 having an outer diameter of 0.295 inches configured to matingly engage the lip 94 of the hollow head 96 of screw 95.

A plurality of torque transmitting structures 101 are provided in lip 102 to facilitate mechanical securement of the sustained release holding device 100 into the hollow head 96 of screw 95. These torque transmitting structures 97, as illustrated in **Fig. 10C**, comprise three Phillips-head receiving portions disposed along a diameter of about 0.236 inches to a depth of between about 0.15 inches. A diameter of the torque transmitting structures 97 may be about 0.048 inches. In accord with previous aspects of the invention, this torque transmitting structure may comprise one or more slots or may comprise other structures conventionally employed to transmit torques. Projecting from a bottom portion of the sustained release holding device 100 is threaded shank 99, which is configured to matingly engage the recessed

threaded portion 98 of the upper portion of the thread shank 91. In the illustrated embodiment, the threaded shank 99 has a length of about 0.10 inches and the threads extend along the shank about 0.06 inches.

Yet another embodiment of the present invention is shown in **Figs. 11A-11B. Fig. 11A** depicts a top view and a cross-sectional view of a screw 103 having a screw head defining a hollow head therein (i.e., a hollow head) 105. A sustained release holding device 124 (see **Fig. 11B**) is detachably insertable within the hollow-head 105 to retain and locally deliver a drug provided therein. Screw 103 also includes a threaded shank 110 for threading the screw 103 comprising the drug delivery system into a bone (not shown). It is generally preferred to position a top surface of the screw 103 substantially flush with the bone, by means of an appropriate screw configuration or by provision of appropriate burr holes.

In this embodiment, similar to the embodiment depicted in **Figs. 10A-10C**, an inside diameter of the hollow head 105 is 0.244 inches and an outer diameter of the hollow head is 0.264 inches. Lip 107 formed at a top portion of the hollow head 105 has an outer diameter of 0.295 inches. The threaded shank 110 is about 0.37 inches in length and possesses, in the illustrated embodiment, a thread 109 having a pitch of 0.69 inches, a root (or minor) diameter of 0.125 inches, and a major diameter of 0.177 inches, wherein the sides of the threads intersect one another at a 30 angle. A tip of the threaded shank 110 is angled, in the illustrated embodiment, at a 30 angle to facilitate insertion.

The interior depth of the hollow head 105 is 0.154 inches. Threaded shank 110 is provided on a bottom portion 104 of the hollow head 105. Formed within an upper portion of the threaded shank 110 and exposed to the hollow head 105 through a torque transmitting structure 108 is a recessed threaded portion 106 having a maximum depth of about 0.28 inches. As shown in **Fig. 11A**, the minimum thread depth of the threaded portion 106 is about 0.09 inches with a thread major diameter of about 0.0595 inches. Torque transmitting

structure 108 is centrally provided in the base portion 110 of the hollow head 105 to facilitate mechanical securement of the screw 103 into a receiving surface, such as a bone. The torque transmitting structure 108 illustrated in **Fig. 11A** comprises a hexagonal key having a diameter of about 0.093 inches and a depth of about 0.125 inches.

Fig. 11B illustrates an embodiment of a sustained release holding device 124 configured for insertion into the hollow head 105 of screw 103. At a bottom portion of the sustained release holding device 124 is a threaded shank 126 corresponding substantially to the opening formed by the torque transmitting structure 108 and recessed threaded portion 106 of screw 103. The threaded shank 126 has a total axial length of about 0.20 inches, of which the threads comprise about 0.085 inches. The threads are configured to matingly engage those of the threaded portion 106 of screw 103 and are not provided in the portion of the threaded shank 126 corresponding to the screw 103 hexagonal key 108.

An outer diameter of the sustained release holding device 124 of **Fig. 11B** is 0.236 inches and the depth is approximately 0.184 inches. The inner diameter of the sustained release holding device 124 is 0.183 inches. At an upper portion thereof is a lip 122 having an outer diameter of 0.295 inches configured to matingly engage the lip 107 of the hollow head 105 of screw 103. A torque transmitting structures 120 is provided in lip 122 and/or hollow cylindrical body 125 of the sustained release holding device 124 to facilitate mechanical securement of the sustained release holding device 124 into the hollow head 105 of screw 103. The torque transmitting structure 120 illustrated in **Fig. 11B** comprises a hexagonal key having a diameter of about 0.1870 inches and a depth of about 0.040 inches.

Fig. 12A is a cross-sectional view of a self-tapping or self-drilling screw 140 in accord with the invention having a screw head defining a hollow head 135 therein. A sustained release holding device 150 (**see Fig. 12F**) is detachably insertable within the hollow head 135 to retain and locally deliver a drug provided therein. Screw 140 also includes a

threaded shank 132 for threading the screw 140 comprising the drug delivery system into a bone. It is generally preferred to position a top surface of the screw 140 substantially flush with the bone, by means of an appropriate screw configuration or by provision of appropriate burr holes. It is preferred, but not necessary, to round or chamfer the transition between the hollow head 135 and the threaded shank 132 to form a shoulder 134. In one aspect thereof, the shoulder 134 is rounded with a radius of 0.09 inches in the transition from the hollow head 135 to a point of inflection in concavity toward a middle portion of the shoulder 134, at which point the shoulder is rounded with a radius of 0.04 inches.

It is preferred that the screw 140 is made of a cleaned and passivated 6AL-4V titanium alloy, although any other surgical grade material of comparable strength, such as but not limited to stainless steel, composites, plastics, and/or ceramics exhibiting sufficient strength and/or hardness to permit insertion into and retention within the selected substrate (e.g., bone). To minimize stresses on the screw 140 and threaded shank 132, a pilot hole may be drilled into the bone.

Corners of the threaded shank 132 are rounded, to about 0.005 inches, to remove sharp corners. Further, all burrs from manufacture are to be removed and all edges are rounded to a minimum of about 0.003 - 0.005 inches. This may be accomplished, for example, by micro bead blasting with S2 bead or by any other conventional surface treatment methods known to those skilled in the art. Further, it is to be understood that the dimensions described and depicted with respect to the illustrated embodiment are not limiting as to any other embodiments of the invention and do not represent, for simplicity of illustration, conventional manufacturing tolerances.

In this embodiment, an inside diameter of the hollow head 135 is 0.244 inches and an outer diameter of the hollow head is 0.264 inches. Lip 137 formed at a top portion of the hollow head 135 has an outer diameter of 0.295 inches. The threaded shank 132 is about 0.39

to 0.41 inches in length and possesses, in the illustrated embodiment, a thread 138 having a pitch of about 0.111 inches and a root (or minor) diameter of about 0.125 inches at the tip of the screw 140, although the geometry of the tip may vary in a manner known to those skilled in the art in accord with the entry or initial drilling conditions expected for a particular application. In the embodiment depicted in **Figure 12D**, the root diameter increases, from the initial root diameter of about 0.125 inches at the tip of the screw 140, by about 0.005 inch per thread up to about 0.135 inches at a base of the thread 138 adjacent the head of the screw. The thread 138 has a major diameter of about 0.250 inches and possesses a thread angle of about 15 ($2\alpha = 30^{\circ}$). As illustrated, the threaded shank 132 has 9 threads per inch. A tip of the threaded shank 132 is smoothly angled, in the illustrated embodiment, at a 45 angle and is radiused at about 0.062 inches.

With respect to the cutting faces or heels of the screw 140 corresponding to the flutes 138, the flutes are radiused at 0.312 inches centered on a perpendicular to the tip of screw 140. As known to those skilled in the art, flutes are longitudinal channels formed in a tap to create cutting edges on the thread profile and to provide chip spaces and cutting fluid passages. The cutting face of the flutes may possess positive, negative, or zero rake, in accord with a desired angular relationship between the cutting face with a radial line through the crest of the tooth at the cutting edge. In this aspect of the invention, two flutes 138 are formed opposite one another as shown in **Fig. 12B.**

As shown in **Fig. 12A**, The interior depth of the hollow head 135 is 0.154 inches. A recessed threaded portion 136, having a maximum depth of about 0.11 inches, is provided at a central portion of a bottom of the hollow head 135. In one aspect, recessed threaded portion 136, as shown in **Fig. 12C**, has a thread depth of about 0.07 inches with a thread diameter of about 0.0595 inches. The overall depth of the threaded portion 136 is about 0.11 inches. The terminus of the recessed threaded portion 136 may comprise a chamfered

portion, as illustrated. Torque transmitting structures 180 are also provided at a bottom of the hollow head 135 to facilitate mechanical securement of the screw 140 into a receiving surface, such as a bone. The torque transmitting structures 180 illustrated in **Fig. 12C** comprise 0.040 inch deep holes having a diameter of about 0.049 inches (± 0.0005) spaced on a diameter of the screw hollow head 135 of 0.161 inches (± 0.0005).

Figs. 12E- 12F illustrate an embodiment of a sustained release holding device 150 configured for insertion into the hollow head 135 of screw 140. A threaded shank 155 is disposed at a bottom portion of the sustained release holding device 150. Threaded shank 155 is configured to matingly engage the opening formed by the recessed threaded portion 136 of screw 140. As shown in **Fig. 12F**, the threaded shank 155 has a total axial length of about 0.065 inches, of which the threads comprise about 0.06 inches to engage a corresponding portion of threaded portion 136 of screw 140.

An outer diameter of the sustained release holding device 150 of **Figs. 12E-12F** is 0.236 inches and the depth of an interior cavity 156 defined thereby is approximately 0.175 inches. The inner diameter of the sustained release holding device 150 is 0.183 inches. At an upper portion thereof is a lip 175 having an outer diameter of 0.295 inches configured to matingly engage the lip 137 of the hollow head 135 of screw 140. Torque transmitting structures 185 are provided in lip 175 of the sustained release holding device 150 to facilitate mechanical securement of the sustained release holding device 150 into the hollow head 135 of screw 140. The torque transmitting structures 185 illustrated in **Figs. 12E-12F** comprise 0.020 inch deep holes having a diameter of about 0.049 inches (± 0.001) spaced on a diameter of the sustained release holding device 150 lip 175 of 0.239 inches (± 0.001).

Figs. 13A- 13B illustrate another embodiment of a sustained release holding device 250 configured for insertion into the hollow head 135 of screw 140. A threaded shank 255 is disposed at a bottom portion of the sustained release holding device 250. Threaded shank

255 is configured to matingly engage the opening formed by the recessed threaded portion 136 of screw 140. As shown in **Fig. 13B**, the threaded shank 255 has a total axial length of about 0.07 inches, of which the threads comprise at least about 0.05 inches to engage a corresponding portion of threaded portion 136 of screw 140.

An outer diameter of the sustained release holding device 250 of **Figs. 13A-13B** is 0.236 inches and the depth of the interior cavity 256 defined thereby is approximately 0.154 inches. The inner diameter of the sustained release holding device 250 is 0.183 inches. At an upper portion thereof is a lip 275 having an outer diameter of 0.295 inches configured to matingly engage the lip 137 of the hollow head 135 of screw 140. The upper surfaces of the sustained release holding device 250 are slightly rounded, having a radius of 0.75.

Torque transmitting structures 285 are provided in lip 275 of the sustained release holding device 250 to facilitate mechanical securement of the sustained release holding device 250 into the hollow head 135 of screw 140. The torque transmitting structures 285 illustrated in **Fig. 13A** comprise recessed portions in the sidewall of the lip 275 that are approximately 0.06 inches deep. As shown, these recessed portions are configured to extend slightly inwardly with increasing depth, at an angle of between approximately 8°- 12°. The torque transmitting structures or recessed portions 285 are, as illustrated, generally semi-circular, possessing a diameter of about 0.049 inches (± 0.001) spaced on a diameter of the sustained release holding device 250 lip 275 of 0.239 inches (± 0.001). Spacing and geometry of the torque transmitting structures or recessed portions 285 may be freely varied to suit the tools and fittings available to produce the torque required to secure the sustained release holding device within the hollow head 135 of screw 140 and may comprise, for example, slots, keys or holes.

The assembled structure of sustained release holding device 250 and the hollow head 135 of screw 140 is depicted in **Figs. 14A-14B**, wherein a drug payload 300 is shown within

the sustained release holding device 250. **Fig. 14C** shows one means of insertion and securement of the drug payload 300 within the sustained release holding device 250. An adhesive 305 is provided along one or more inner surfaces of the sustained release holding device 250 prior to insertion of the drug payload 300. Upon insertion of the drug payload 300, the adhesive 305 sets and retains the drug payload in place. Although it is preferred that the adhesive 305 have a low enough viscosity to permit the adhesive to flow into gaps between the drug payload 300 and the inner surfaces of sustained release holding device 250, this property is not required and any adhesive 305 compatible with the drug payload coating layer or rate-limiting barrier 315, the drug itself, and/or the material of the sustained release holding device 250, corresponding to various embodiments of the invention, is acceptable.

In accord with the invention, the adhesive 305 may be one that can be applied, at room temperature, by a physician, veterinarian, or medical worker, in accord with the application to facilitate flexibility of drug payload 300 selection and application. It is also possible, in accord with the invention, to pre-form frequently applied drug payloads 300 within the sustained release holding device 250 to simplify ease of end use by a physician, veterinarian, or medical worker. Such pre-formed combinations of drug payload 300 and screw 140 could permit additionally permit utilization of other means of adhesive affixation, including thermosetting resins or compounds. However, any adhesive process utilizing elevated temperatures would have to selected so as not to materially degrade either the coating of the drug payload 300 or the drug contained therein, as the efficacy of various drugs have been shown to be adversely affected by elevated temperatures. Further, such pre-formed combinations of drug payloads 300 and screw 140 would require some adjustment to the structures and methods provided herein to permit the screw 140 to be inserted into the target substrate (e.g., bone) by application of torque directly to the head or upper portion of the screw or of an upper portion of the sustained release holding device (e.g., 250). In other

words, torque transmitting structures 285 can be disposed within or integrated into the head or upper portion of the screw 140 or sustained release holding device 250 in a manner known to those skilled in the art.

Once implanted, the drug payload 300 is released at a controlled rate over an extended period of time, in accord with the intended therapeutic result, into the area of the patient's body surrounding the insertion site as represented in **Fig. 14D**. The release rate may be controlled, for example, by appropriate variance of coating layer or rate-limiting barrier 315 properties and geometry. The coating layer 315, such as but not limited to a polymer coating layer, may be selectively omitted, entirely or partially, from one or more portions of the surface area of the drug to be delivered, particularly from the drug surface adjacent the outlet of the sustained release holding device 250. In one aspect thereof, the coating layer 315 may be applied only to a surface of the drug payload 300 adjacent the opening of the sustained release holding device 250. In such an embodiment, adhesive 305 should be selected so as not to structurally or chemically degrade the drug(s) present in the drug payload 300.

In still another aspect thereof, the coating layer 315 may be applied to a surface of the drug payload 300 adjacent the opening of the sustained release holding device 250 and to an opposing surface adjacent adhesive 305, wherein the adhesive is selected by volume and/or viscosity to limit flow of the adhesive to adjoining surfaces of the drug payload not having a coating layer.

One device suitable for use in installing an embodiment of the drug delivery system of the invention is depicted in **Figs. 15A-15B**. The drill imparting the torque to the screw may comprise essentially any automated, motorized, or manual drill considered acceptable by medical practitioners for medical applications. In one aspect of contemplated surgical procedures, the area of implantation is made accessible by movement of soft tissues away from the targeted area and a conventional hand held drill may be used. In other aspects

thereof, to minimize trauma to the tissues, less invasive procedures are used and the drill bit 405 may be advantageously provided within a cannula or drill sleeve, such as those conventionally applied during arthroscopic or orthroscopic surgery, to prevent damage to soft tissue during drilling.

Figs. 15A-15B illustrate different embodiments drivers 450 configured to drive screw 140 into the preformed pilot holes 410, 420 as discussed later with respect to **Fig. 16A**. Each driver 450 has a head 460 configured to matingly engage torque transmitting structures 180 on the interior portion of hollow head 135. As depicted in **Figs. 15A-15B**, the head 460 comprises three drive members 465 approximately 0.040 inches in length having a diameter of about 0.049 inches spaced on a diameter of 0.161 inches to correspond with the screw 140 depicted in **Figs. 12A-12F**. The drive members 465 can assume any shape, number or distribution corresponding to that of the torque transmitting structures 180 of the hollow head 135. In operation, the drive shaft 470 of the driver 450 is rotated clockwise or counterclockwise, at a proximal end, to produce a corresponding clockwise or counterclockwise motion of the head 460 at a distal end. The proximal end of the driver 450 may, as shown in **Fig. 15A** have a knob 475 having a radius configured to permit generation of varying degrees of torque in accord with a moment arm applied by a medical provider's digital manipulation. Alternatively, as shown in **Fig. 15B**, the drive shaft itself may simply be provided with a high friction or grippable surface 480 having a diameter substantially equal to the diameter of the drive shaft 470 itself to permit less torque than the driver 450 depicted in **Fig. 15A** to thereby enable a finer degree of control and tactile sensitivity. Although the drivers 450 depicted are manually operated, the drivers 450 may advantageously be motorized.

A method for implanting a drug delivery device in accord with **Figs. 14A-14D** into a bone is depicted in **Figs. 16A-16G**.

First, as shown in **Fig. 16A**, it is preferred to drill a pilot hole into the bone 400. Alternatively, a self-tapping or self-drilling screw may be used. The drill bit 405 depicted in **Fig. 16A** produces a first pilot hole 410 having a first depth and first diameter D1 and a second pilot hole 420 having a second depth and a second diameter D2. The first diameter D1 is selected to less than the outer diameter of the threaded shank 132 (i.e., less than 0.25 inches in the embodiment of **Fig. 12A**) and is preferably less than or equal to the root diameter of the threaded shank 132 (i.e., less than 0.135 inches in the embodiment of **Fig. 12A**) or of the tip of the screw 140 (i.e., less than the initial root diameter of about 0.125 inches in the embodiment of **Fig. 12A**) to permit effective securement of the threaded shank 132 into the bone 400.

An intermediary portion 415 between the first diameter and the second diameter is preferably chamfered or angled to correspond to the shape of the shoulder 134 of the screw 140. An abrupt step-change in diameter may, however, also be used in accord with a screw so configured in accord with the invention. Second diameter D2 of pilot hole 420 is configured to substantially correspond to an outer diameter of the hollow head 135 of the screw 140. Although not shown, drill bit 405 may comprise a third section configured to drill a relatively shallow third hole having a thickness corresponding to a thickness of the lip 137 of the hollow head 135. In this way, an upper edge of the lip and hollow head may be provided flush with the surface of the bone.

Fig. 16B illustrates a step of connecting the screw 140 of **Fig. 12A** and the driver 450 of **Fig. 15A** in accord with the invention. **Fig. 16C** illustrates insertion of the screw 140 into the pilot holes 410, 420 drilled into the bone 400 by applying a torque to the driver 450 drive shaft 470 by means of the knob 475. **Fig. 16D** depicts the screw 140 inserted into the bone 400.

Following insertion of the screw 140, the drug payload 300 is inserted in accord with the aspect of the invention depicted in **Fig. 14C**, wherein a health care provider first places an adhesive material 305 on at least one surface of the inner walls of the sustained release holding device (e.g., 250) and, second, presses the drug payload against the adhesive to secure the drug payload within the sustained release holding device.

Once the drug payload 300 is secured within the sustained release holding device 250 and following lapse of a setting time for the adhesive, if necessary, the sustained release holding device 250 may be inserted into the hollow head 135 of screw 140, as shown in **Figs. 16E-16G**. **Fig. 16E** illustrates a step of connecting the sustained release holding device 250 of **Figs. 13A-13B** and a driver 550 substantially similar to that of driver 450 **Fig. 15A**. In this particular embodiment of driver 550, the distal end 590 has a raised portion or boss 555 configured to engage the inside of lip 275 of the sustained release holding device 250. This engagement is accomplished by rotating knob 575 clockwise to retract the drive shaft 570 linearly away from distal end 590 using threads 580 to convert the rotary motion to a linear motion.

The inner diameter ID of distal end 590 between points A1 and A2, as depicted in **Fig. 16F**, is substantially constant and is greater than an outside diameter OD of the driver head 560. The inner diameter ID of distal end 590 at point A2 is substantially equal to an outside diameter OD of the driver head 560. The inner diameter ID of distal end 590 between points A2 and A3, as depicted in **Fig. 16F**, decreases with increasing distance from the front or leftmost of distal end, as shown, and is less than an outside diameter OD of the driver head 560. Therefore, as the driver head 560 is withdrawn past point A2, the driver head exerts an outward force against the inner walls of the distal end 590. The narrowed portion 585 adjacent the distal end 590 facilitates outward flexure of the distal end walls, including the raised portion or boss 555.

Accordingly, when driver head 560 is retracted, boss 555 is splayed outwardly to engage the inside of lip 275 of the sustained release holding device 250 and secure the sustained release holding device to the driver 550 as shown in **Fig. 16F**. Once secured, the sustained release holding device 250 is placed within the hollow head so that the threaded shank 225 is adjacent to and in initial contact with the threaded portion 136. Driver 550 is then itself rotated clockwise to screw the threaded shank 225 into the threaded portion 136 to secure the sustained release holding device 250 in the hollow head 135.

Engagement between the boss 555 and the lip 275 of sustained release holding device 250 is then released by rotating knob 575 to linearly advance driver head 560 and return the outwardly splayed boss 555 to its original or equilibrium position, whereupon it does not contact the lip 275. The driver 550 may then be removed, leaving the installed bone screw 140 bearing a drug payload 300 in sustained release holding device 250, as shown in **Fig. 16G**.

The purpose of the above description and examples is to illustrate some embodiments of the present invention without implying any limitation. It will be apparent to those of skill in the art that various modifications and variations may be made to the method and device of the present invention without departing from the spirit or scope of the invention. All patents and publications cited herein are incorporated by reference in their entireties.

The Claims

What is claimed is:

1. A method for locally administering a therapeutically effective compound to a joint of a mammal, the method comprising the step of:

intraarticularly implanting a sustained release device to deliver the therapeutically effective compound within a synovial capsule of the joint such that synovial fluid concentration of the compound is greater than plasma concentration of the compound during substantial lifetime of the device.

2. The method of claim 1, wherein the plasma concentration is substantially non-toxic.

3. The method according to claim 1, wherein the synovial fluid concentration is therapeutic.

4. The method according to claim 1, wherein the device releases the therapeutically effective compound for at least 8 weeks.

5. The method according to claim 1, wherein the device releases the therapeutically effective compound for at least 12 months.

6. The method according to claim 1, wherein the device releases the therapeutically effective compound for about 3 years.

7. The method according to claim 1, wherein the synovial fluid concentration of the compound remains several orders of magnitude greater than the plasma concentration over the lifetime of the device.

8. The method according to claim 1, wherein the therapeutically effective compound is fluocinolone acetonide.

9. The method according to claim 1, wherein the therapeutically effective compound is a cyclosporine.

10. A method for treating arthritis of joint, the method comprising the step of:

intraarticularly implanting a sustained release device into a joint to deliver a therapeutically effective compound within a synovial capsule of the joint such that synovial fluid concentration of the compound is greater than plasma concentration of the compound during substantial lifetime of the device.

11. An implantable sustained release device for locally administering a drug, the device comprising:

a bone screw including a hollow portion configured to receive a sustained release holding device, said sustained release holding device itself configured to receive a drug payload.

12. An implantable sustained release device in accord with claim 11, wherein the sustained release holding device is removably provided within said hollow portion.

13. An implantable sustained release device in accord with claim 12, further comprising:

a drug payload including one or more drugs;

a rate-limiting barrier configured to limit a release rate of a drug from the drug payload to thereby provide sustained release of the drug.

14. An implantable sustained release device in accord with claim 13,

wherein the rate-limiting barrier is configured to provide a steady-state release rate of a drug from the drug payload substantially equal to a steady-state rate of elimination of the drug from a treatment site, and

wherein the rate-limiting barrier is configured to provide a predetermined therapeutic concentration of the drug in the treatment site, said predetermined therapeutic concentration of the drug being greater than a plasma concentration of the drug until substantially all of the drug in the drug payload is depleted.

15. A system comprising:

a mechanical member attachable to a portion of a body;

a first chamber having an opening configured to receive a sustained release device;

a sustained release device; and

a removably attachable retainer for retaining the sustained release device in the first chamber.

16. The system according to claim 15, wherein the mechanical member is substantially rigid and is configured for at least partial insertion into a bone.

17. The system according to claim 16, wherein the mechanical member comprises a screw.

18. The system according to claim 17, wherein the first chamber is defined within a head of the screw.

19. The system according to claim 18, wherein the sustained release device comprises a drug-bearing insert attachable within said first chamber.

20. The system according to claim 19, wherein the drug-bearing insert insert is removably attachable within said first chamber by a mechanical fastener.

21. The system according to claim 15, wherein the sustained release device comprises an inner core comprising an effective amount of a low solubility agent; and

a non-bioerodible polymer coating layer, the polymer layer being permeable to the low solubility agent, wherein the polymer coating layer covers the inner core and is essentially non-release rate limiting.

22. The system according to claim 15, wherein said removably attachable retainer partially occludes the chamber opening.

23. A system comprising:

a mechanical member attachable to a portion of a body;

a chamber disposed within the mechanical member configured to receive a sustained release device bearing at least one drug; and

an opening in the chamber to permit release of the at least one drug borne by the sustained release device.

24. The system according to claim 23, further comprising a sustained release device configured for placement in said chamber of said mechanical member.

25. The system according to claim 24, wherein the sustained release device comprises an inner core comprising an effective amount of at least one low solubility agent; and

a non-bioerodible polymer coating layer, the polymer layer being permeable to the at least one low solubility agent, wherein the polymer coating layer covers the inner core and is essentially non-release rate limiting.

26. The system according to claim 25, wherein the mechanical member is substantially rigid and is configured for at least partial insertion into a bone.

27. The system according to claim 26, wherein the mechanical member comprises a screw.

28. The system according to claim 27, wherein the chamber is defined within a head of the screw.

29. A method for administering a drug to a joint, the method comprising the step of:

positioning a mechanical member in or adjacent a bone, said mechanical member configured to hold a sustained release drug delivery device bearing at least one drug; and

outputting said at least one drug from said sustained release drug delivery device at a substantially controlled rate.

30. The method of claim 29, wherein the drug comprises a steroid.

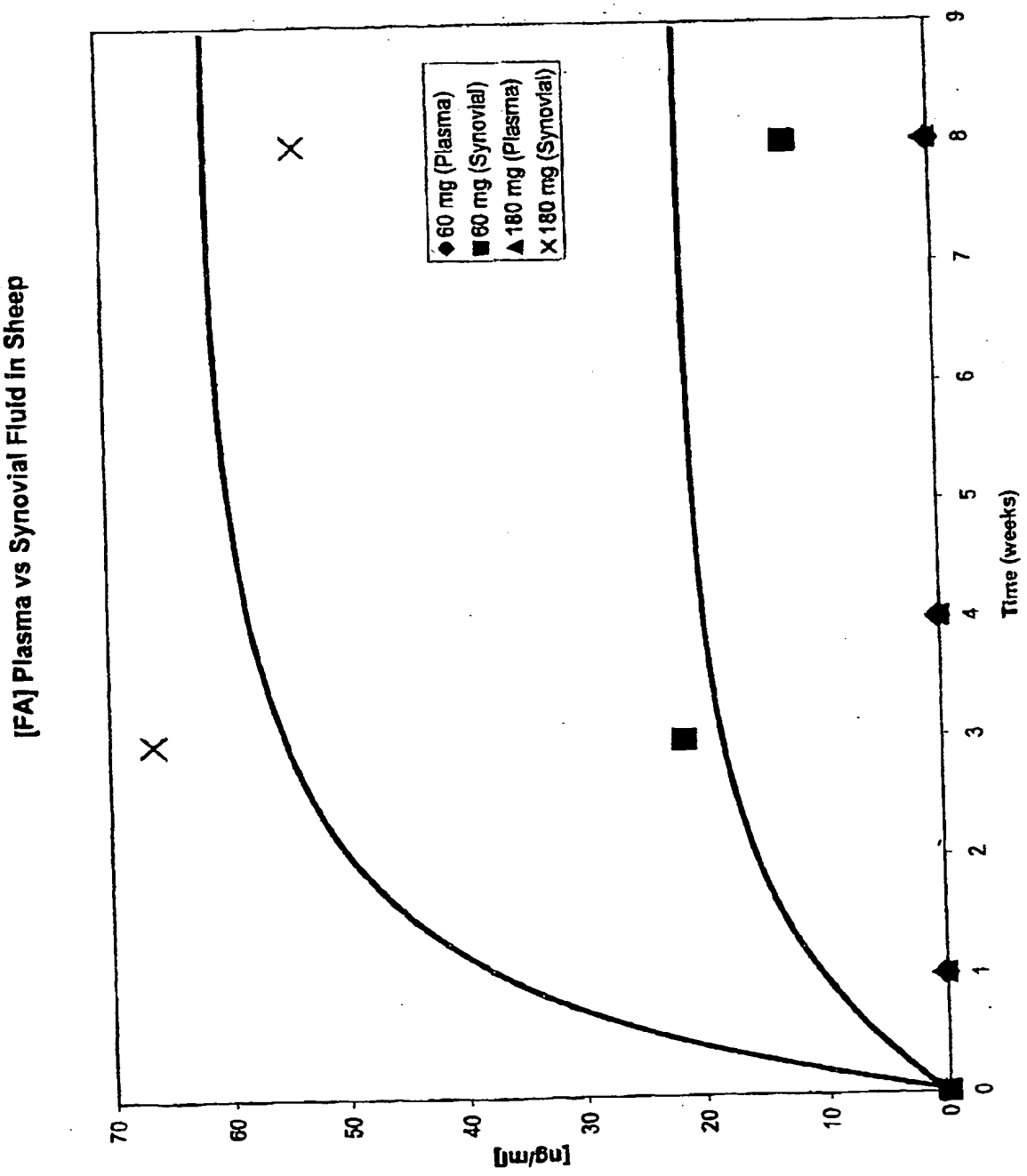


FIG. 1

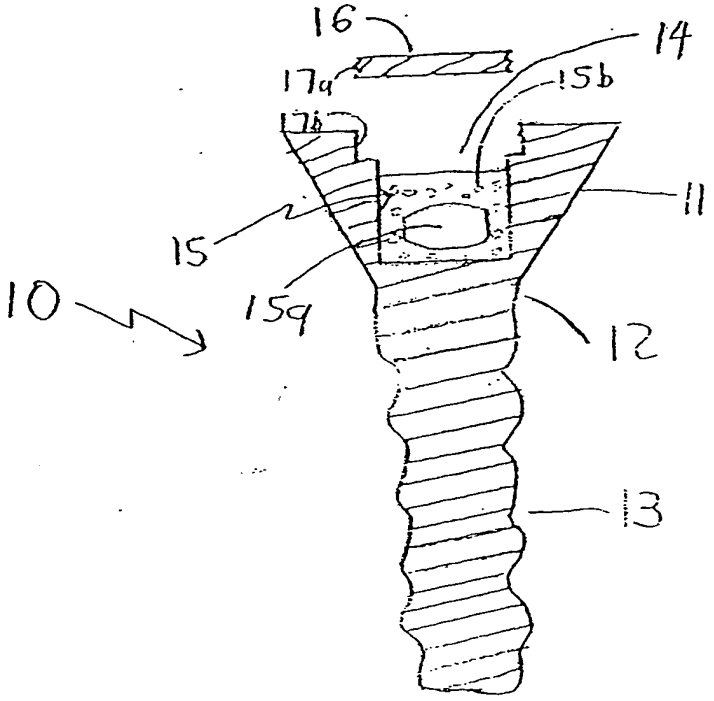


FIG. 2A

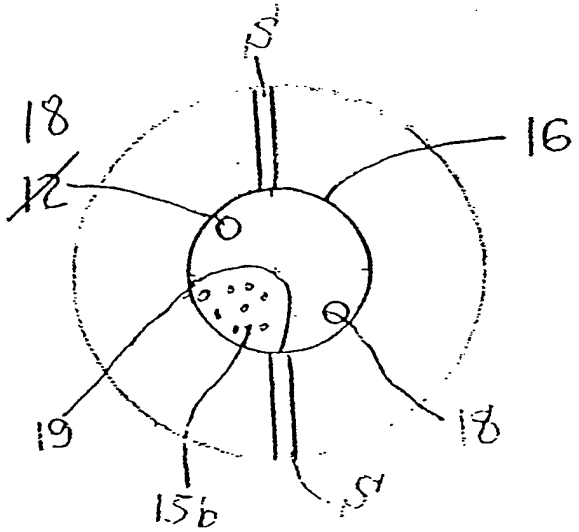


FIG. 2B

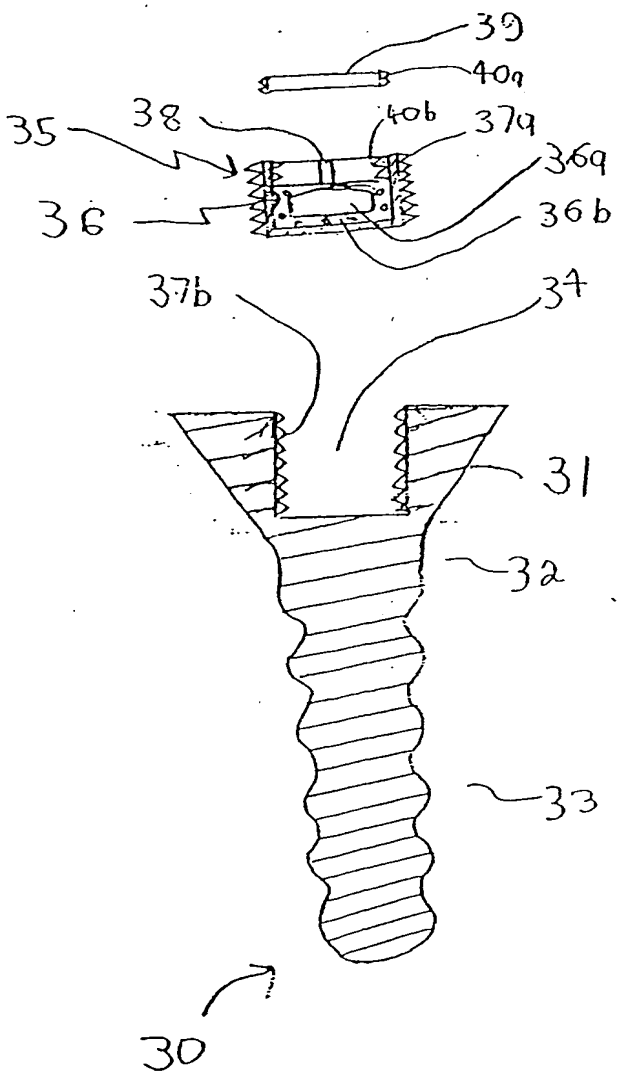


FIG. 3

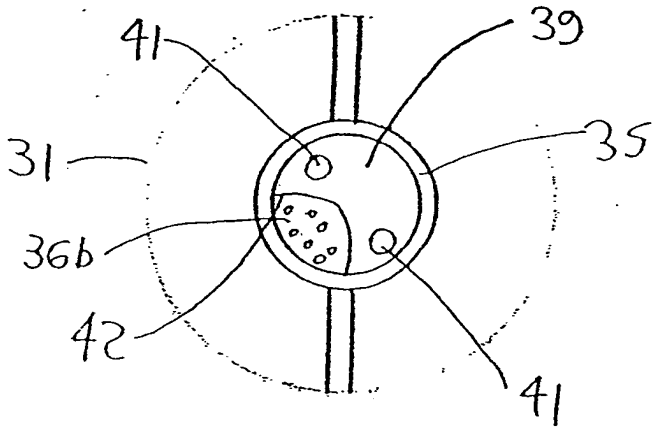


FIG. 4

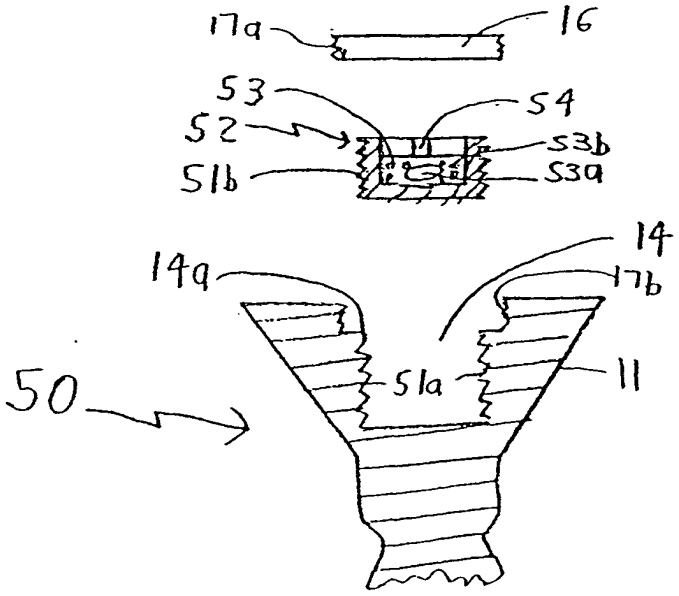


FIG. 5

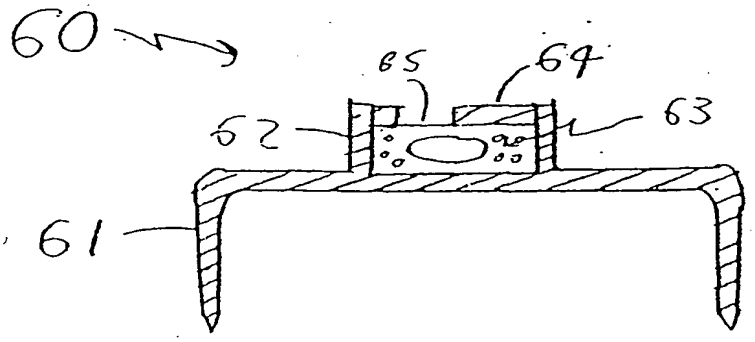


FIG. 6

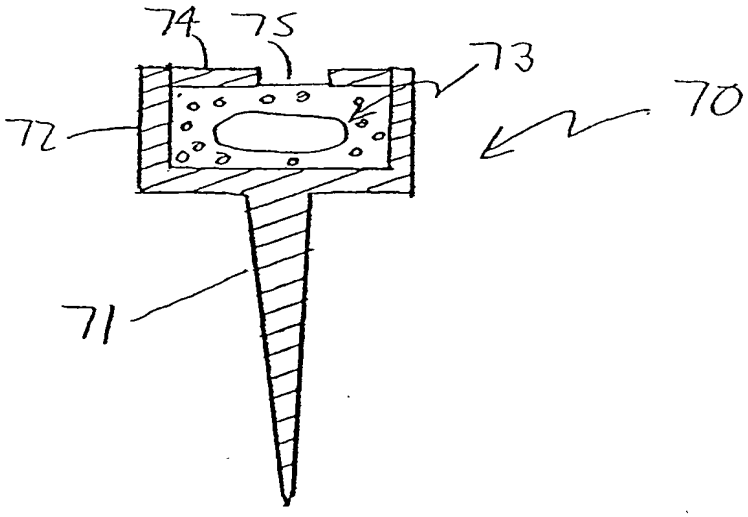


FIG. 7

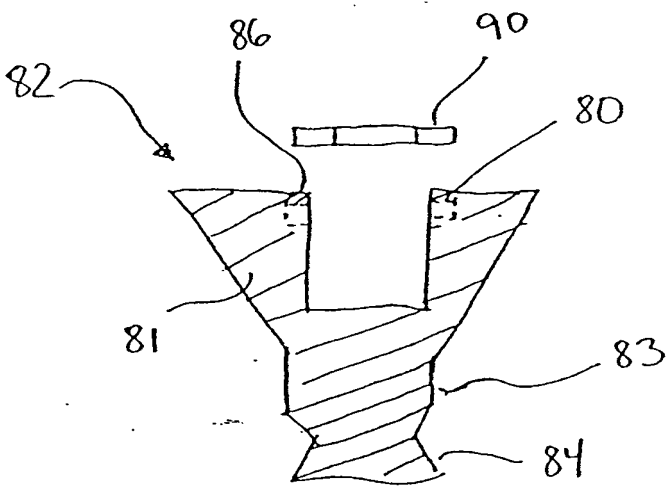


FIG. 8

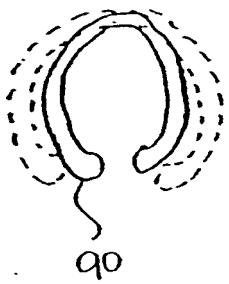


FIG. 9B

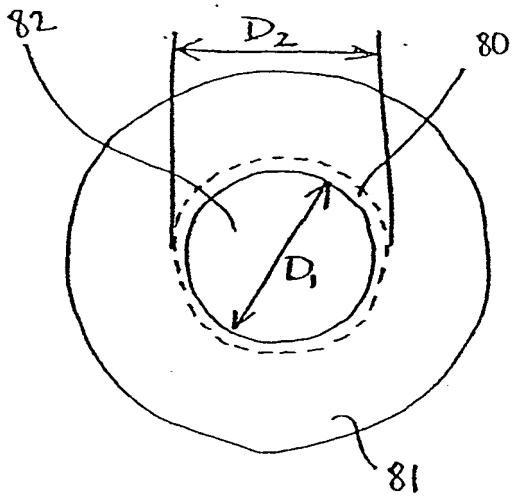


FIG. 9A

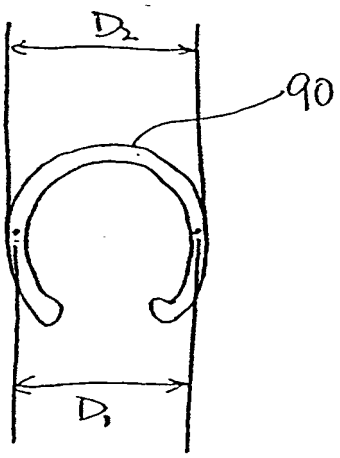


FIG. 9C

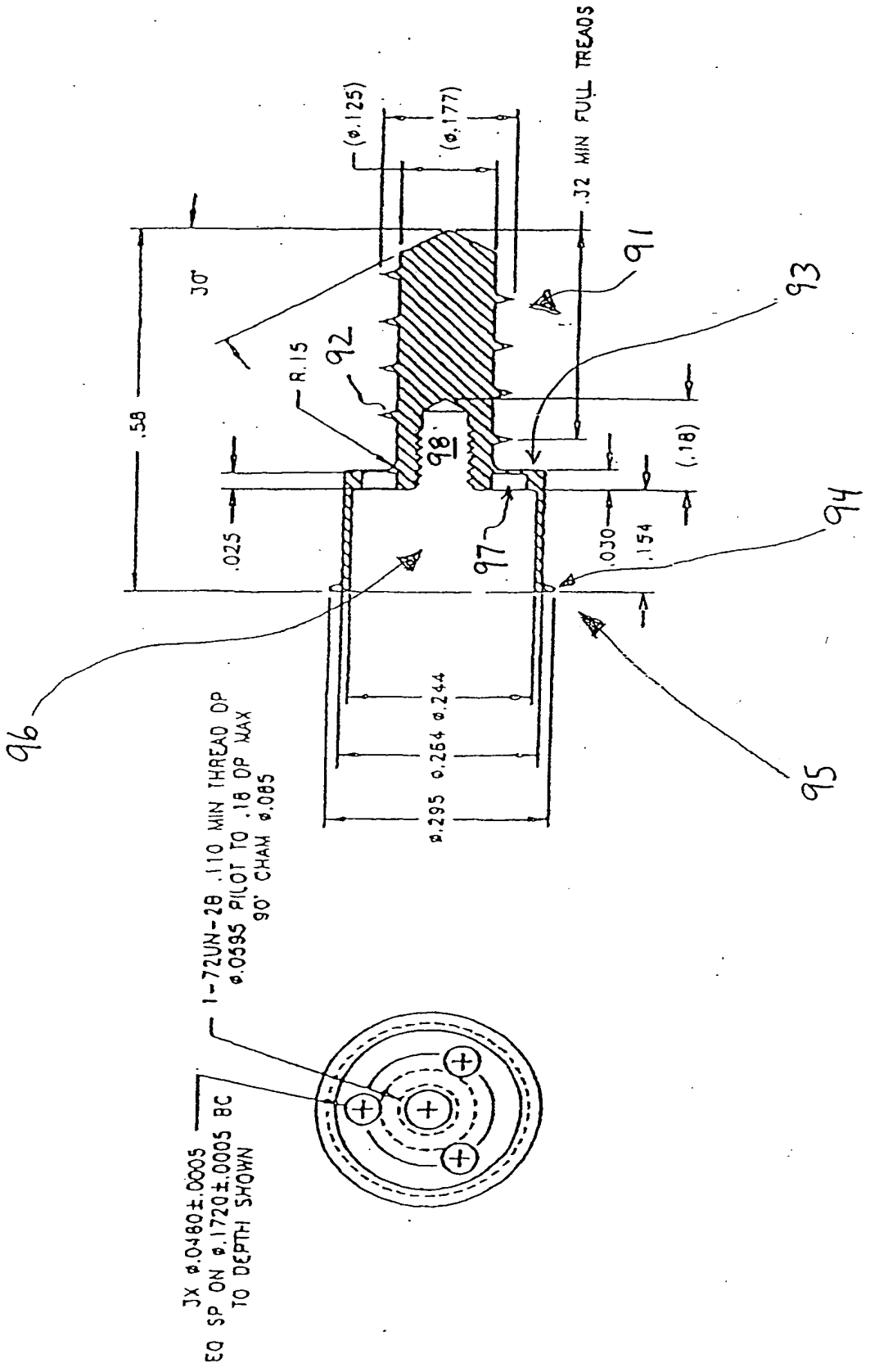

(ø.125)
(ø.177)
.32 MIN FULL TREADS
30°
.58
R.15
92
91
93
98
(.18)
.025
97
.030
.154
94
96
95
ø.295 ø.264 ø.244
1-72UN-2B .110 MIN THREAD DP
ø.0595 PILOT TO .18 DP MAX
90° CHAM ø.085
JX ø.0480±.0005
EQ SP ON ø.1720±.0005 BC
TO DEPTH SHOWN

Figure 10A

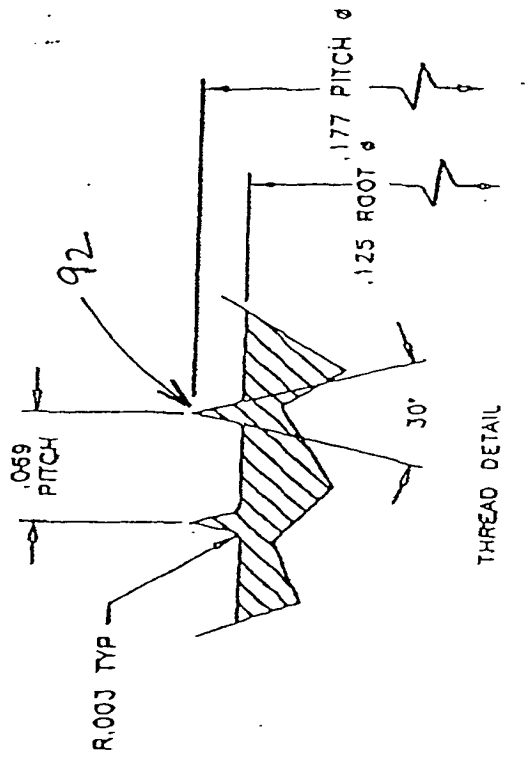


Figure 10B

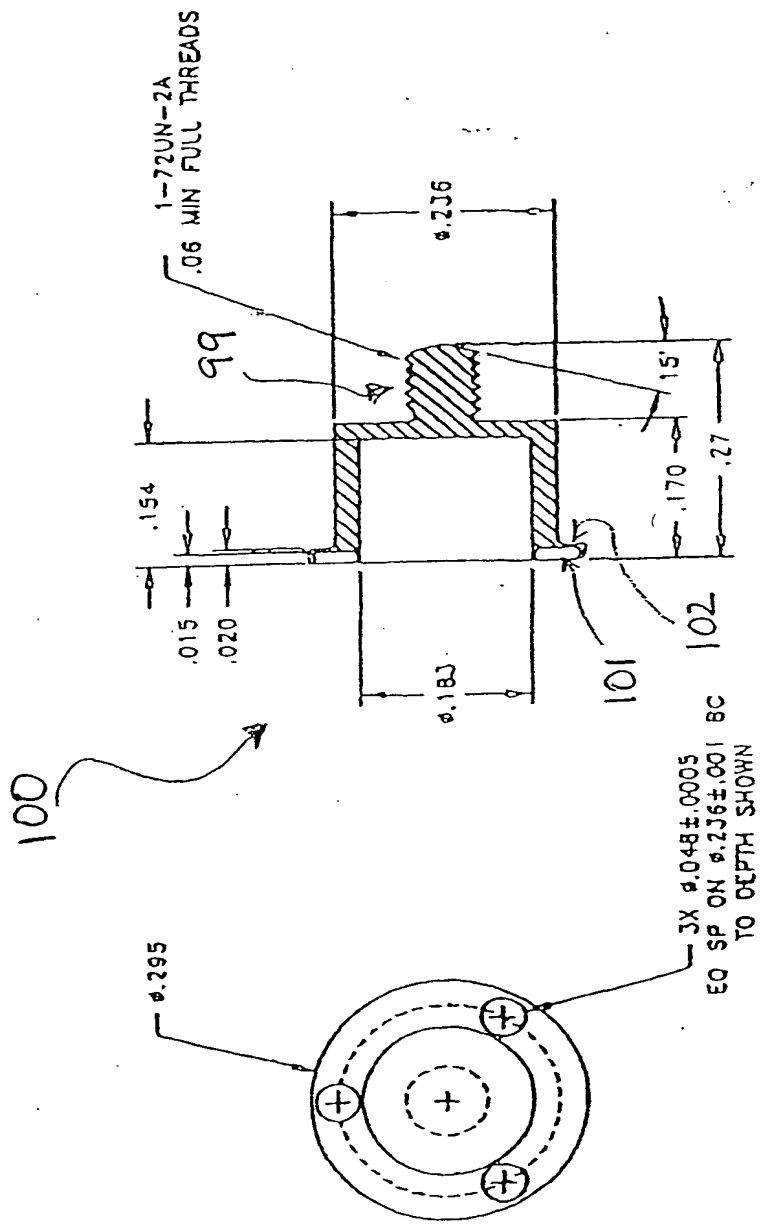

1-72UN-2A
.06 MIN FULL THREADS
ø.236
99
15°
.154
.170
.27
.015
.020
ø.183
101
102
100
3X ø.048±.0005
EQ SP ON ø.236±.001 BC
TO DEPTH SHOWN
ø.295

Figure 10C

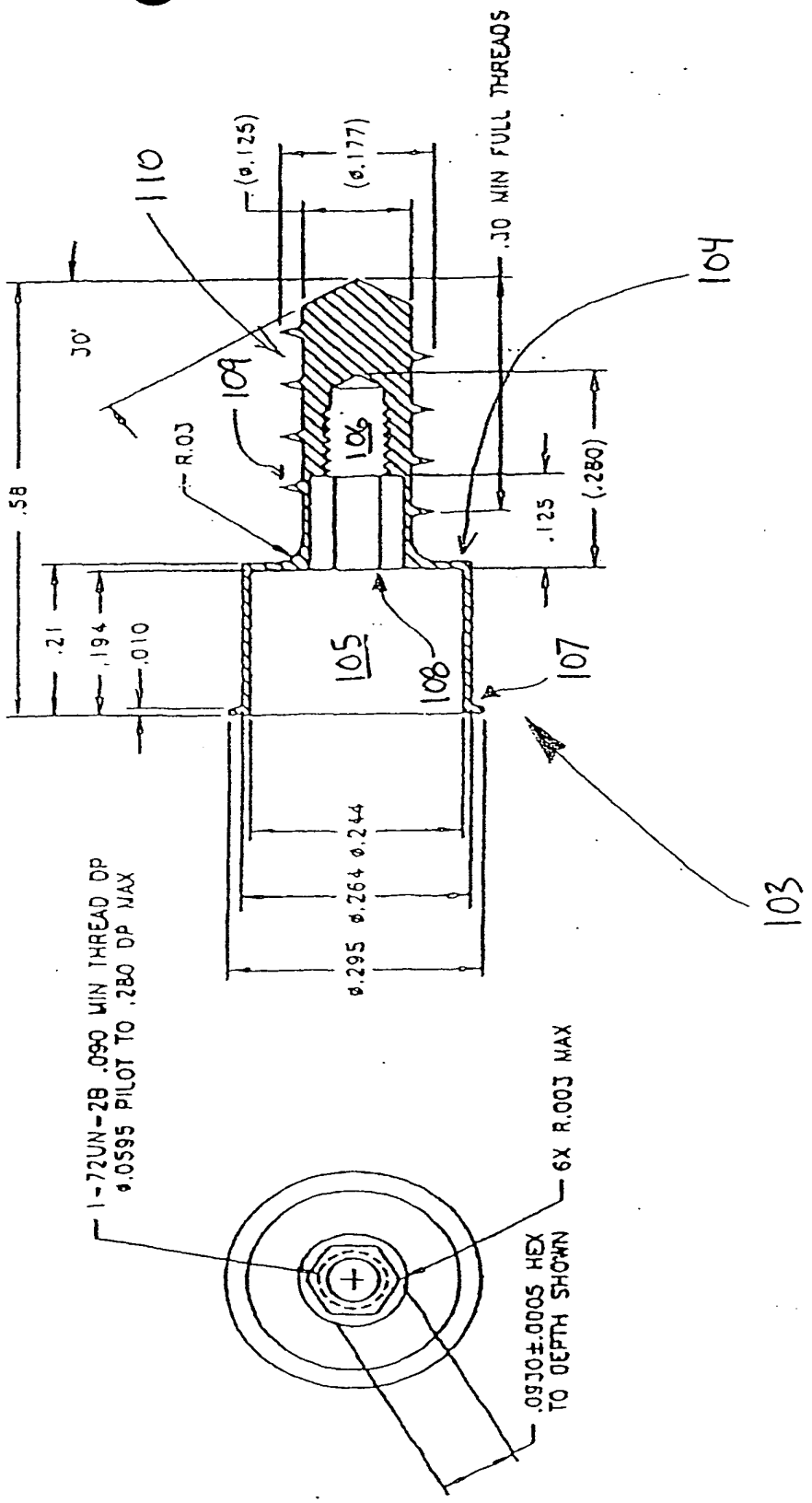


Figure 11A

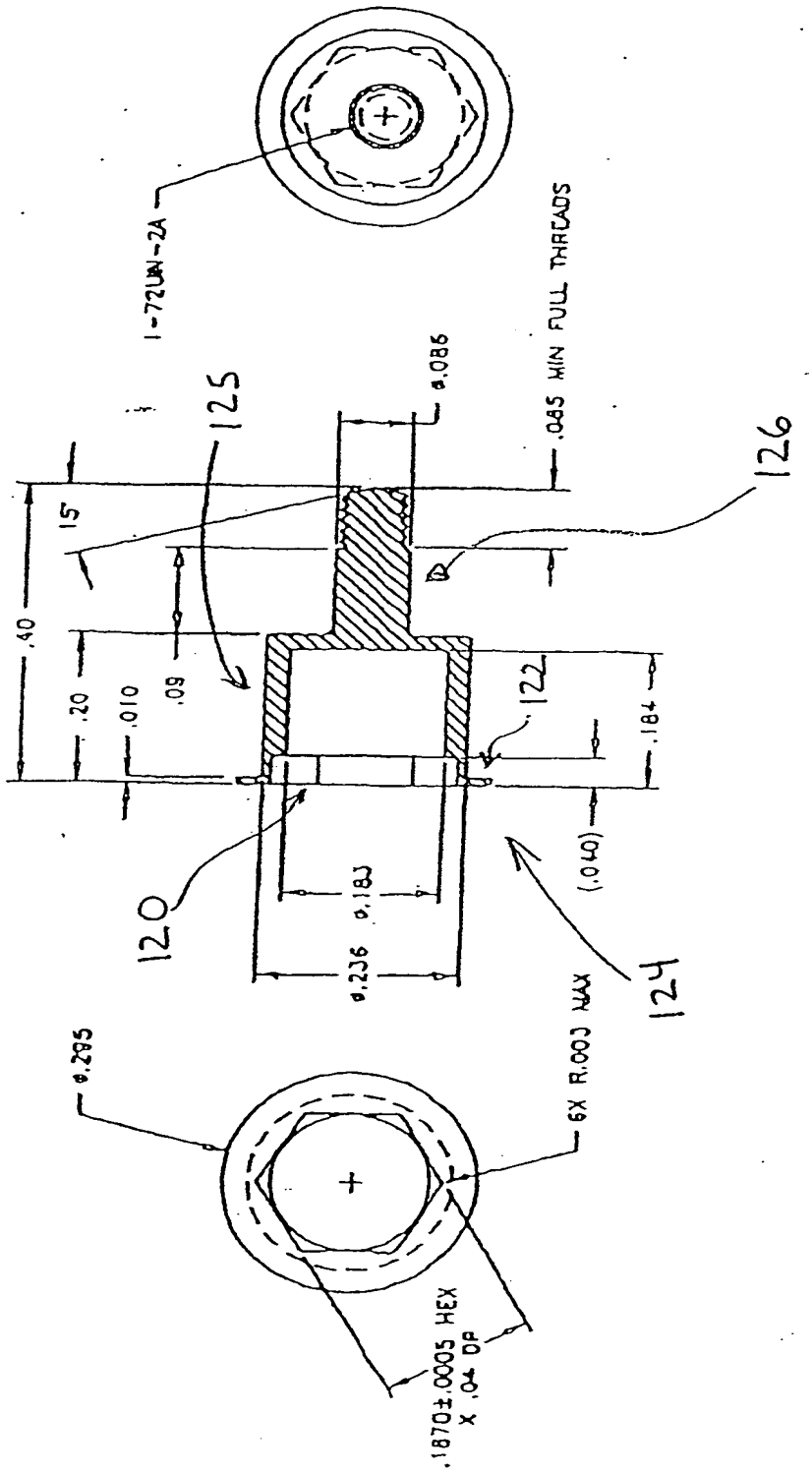


Figure 11B

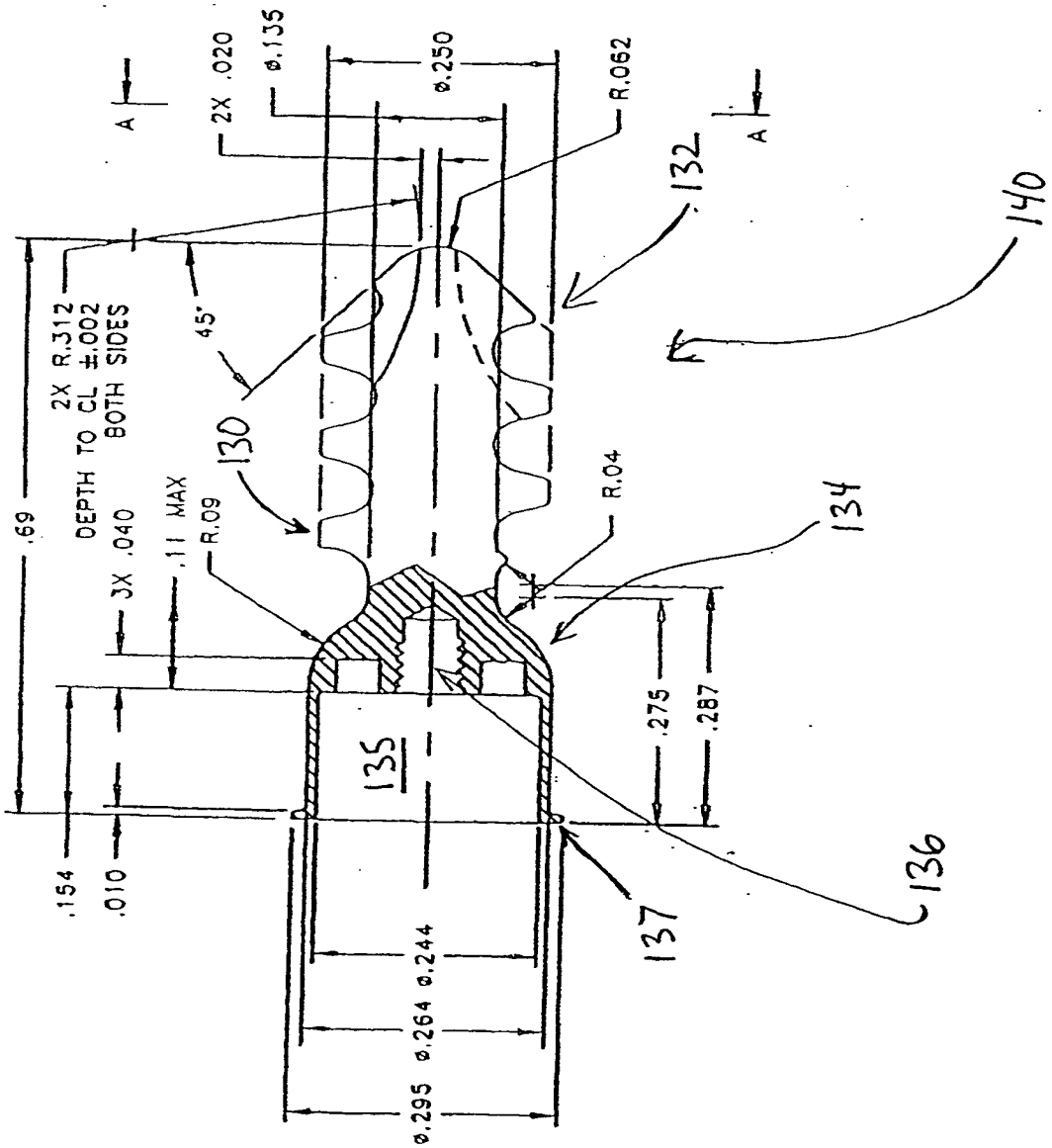


Figure 12A

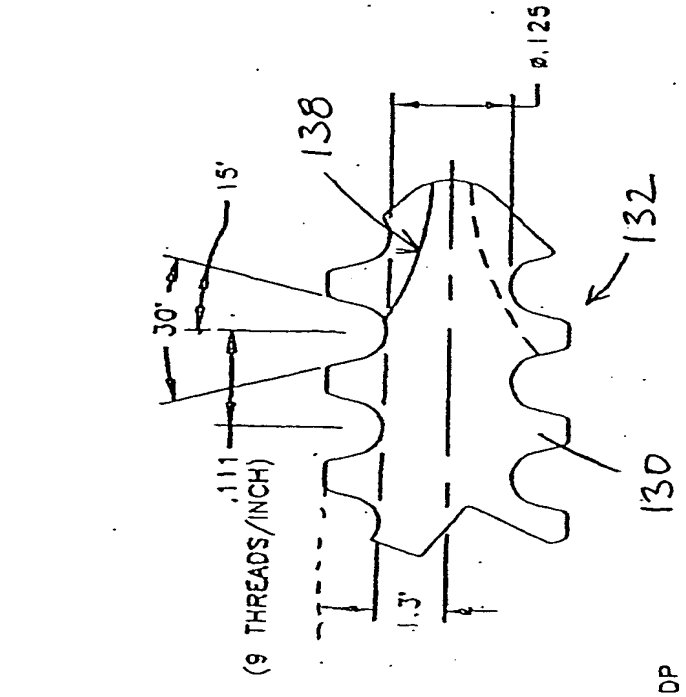


Figure 12D

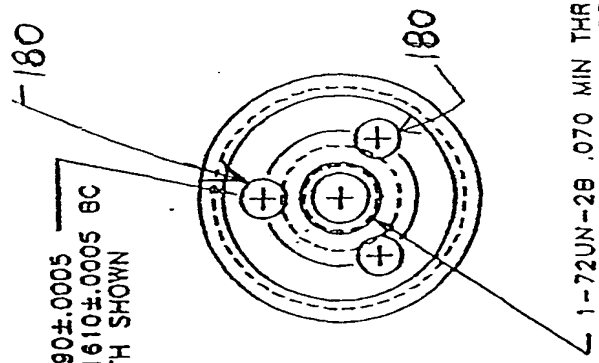


Figure 12C

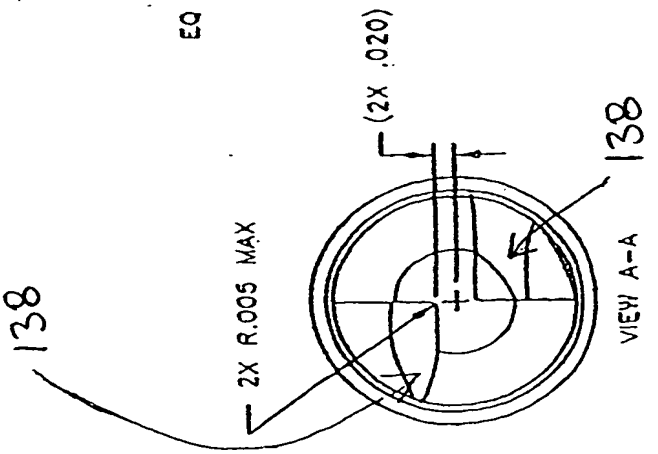


Figure 12B

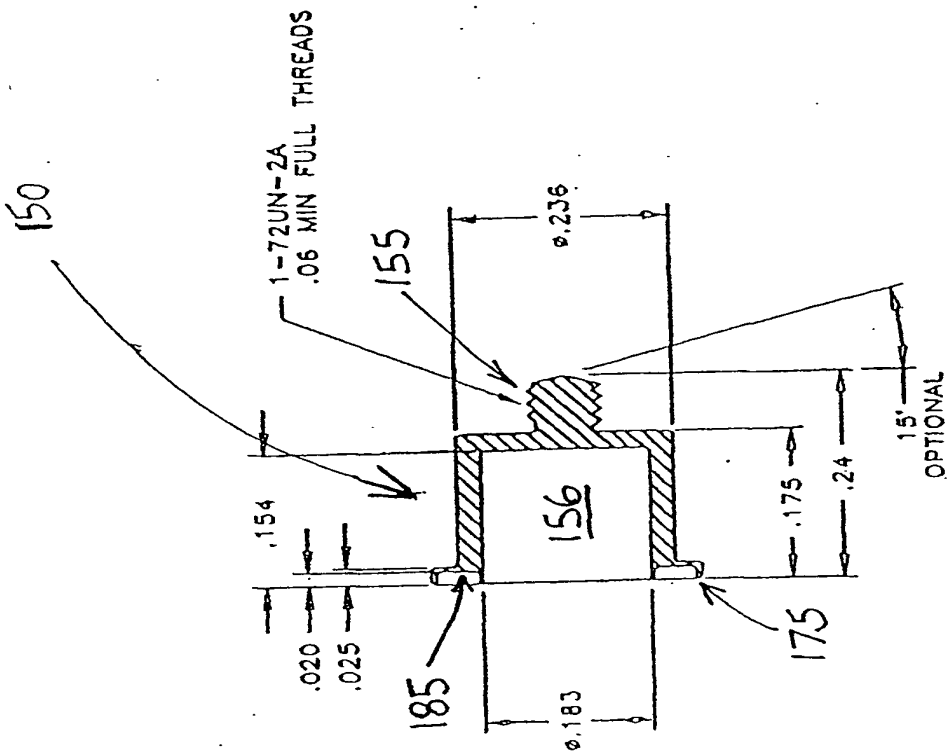


Figure 12F

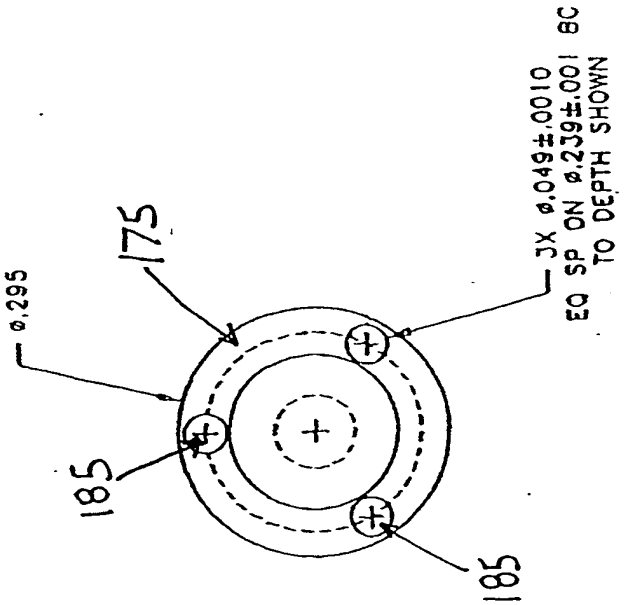


Figure 12E

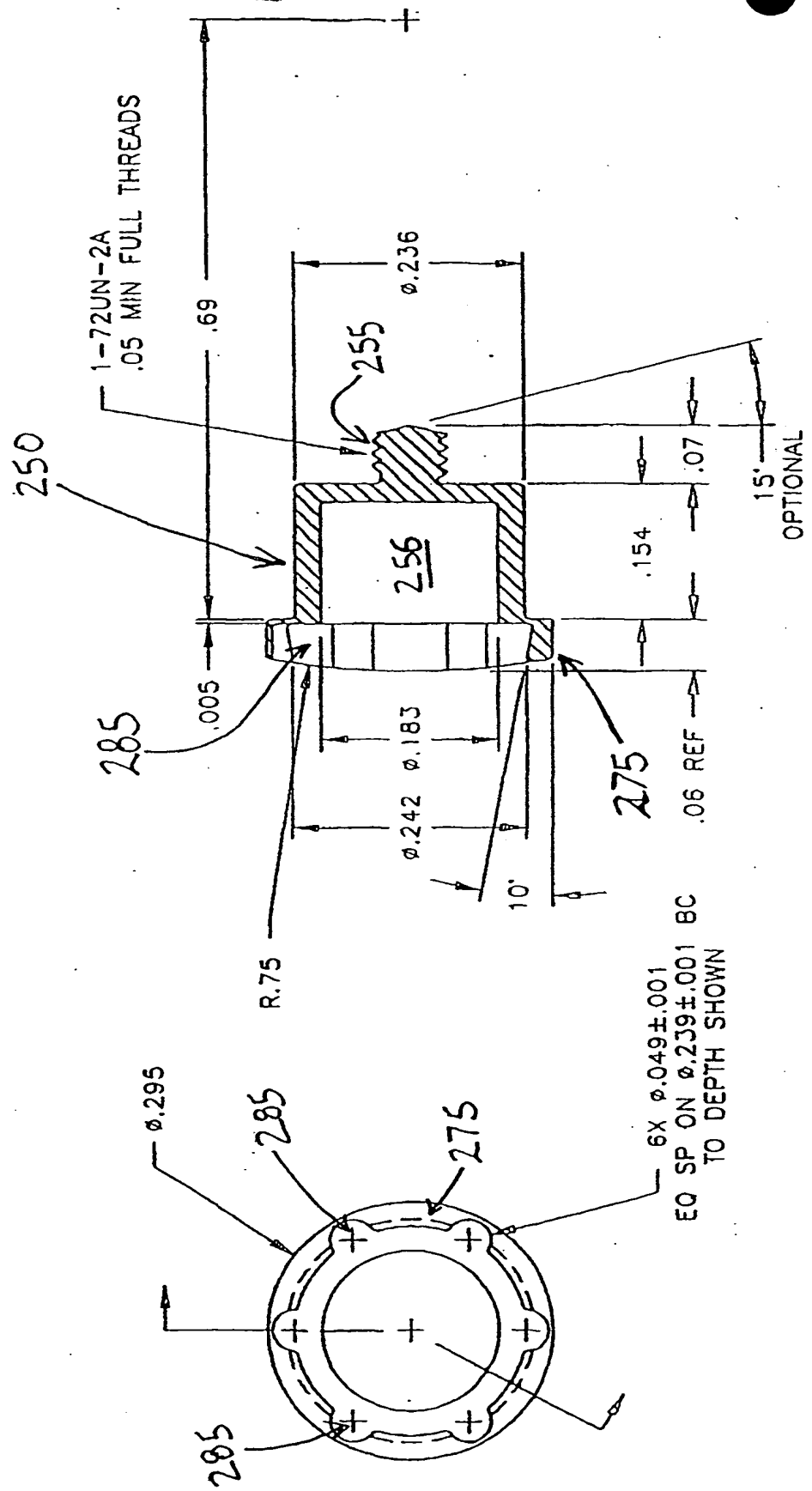


Figure 13B

Figure 13A

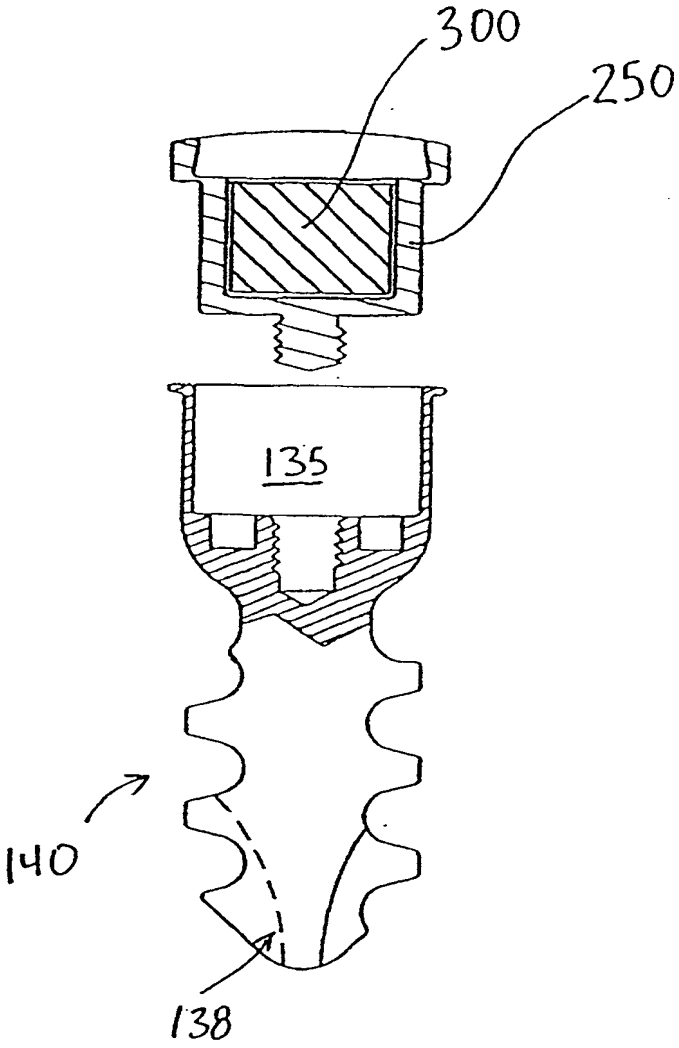


Figure 14A

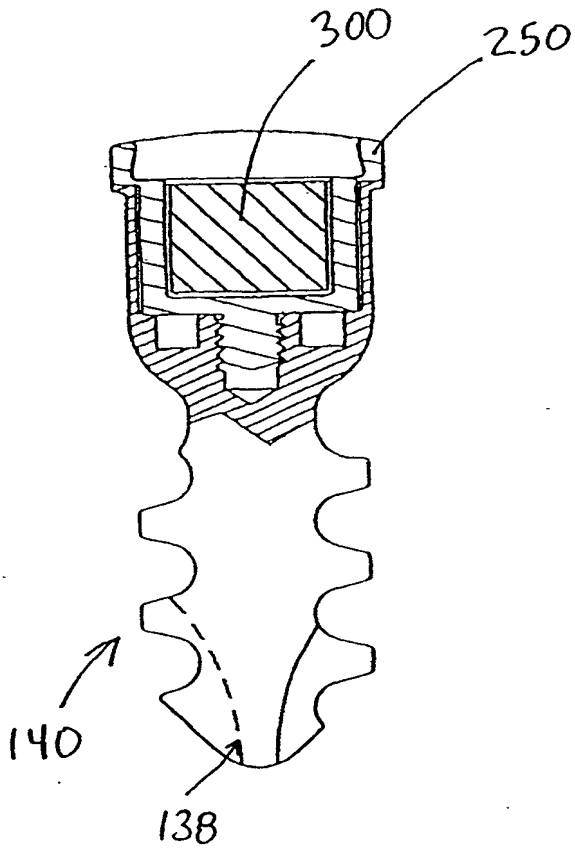


Figure 14B

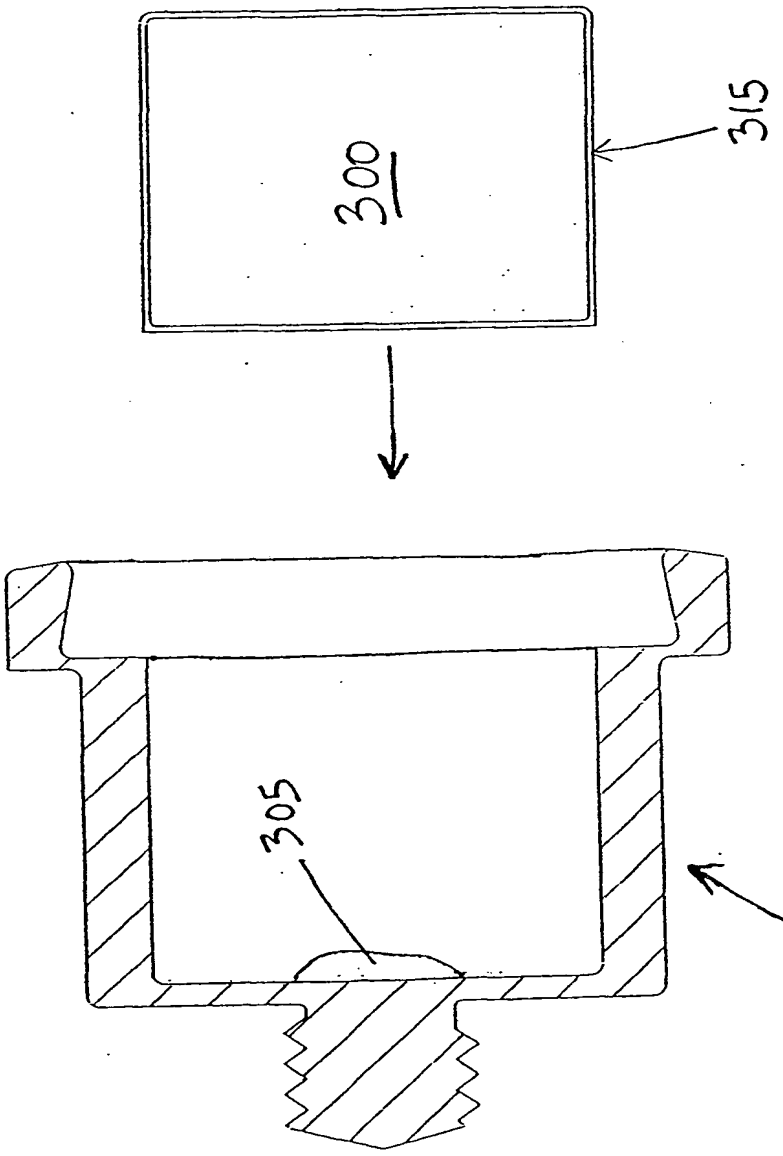


Figure 14C

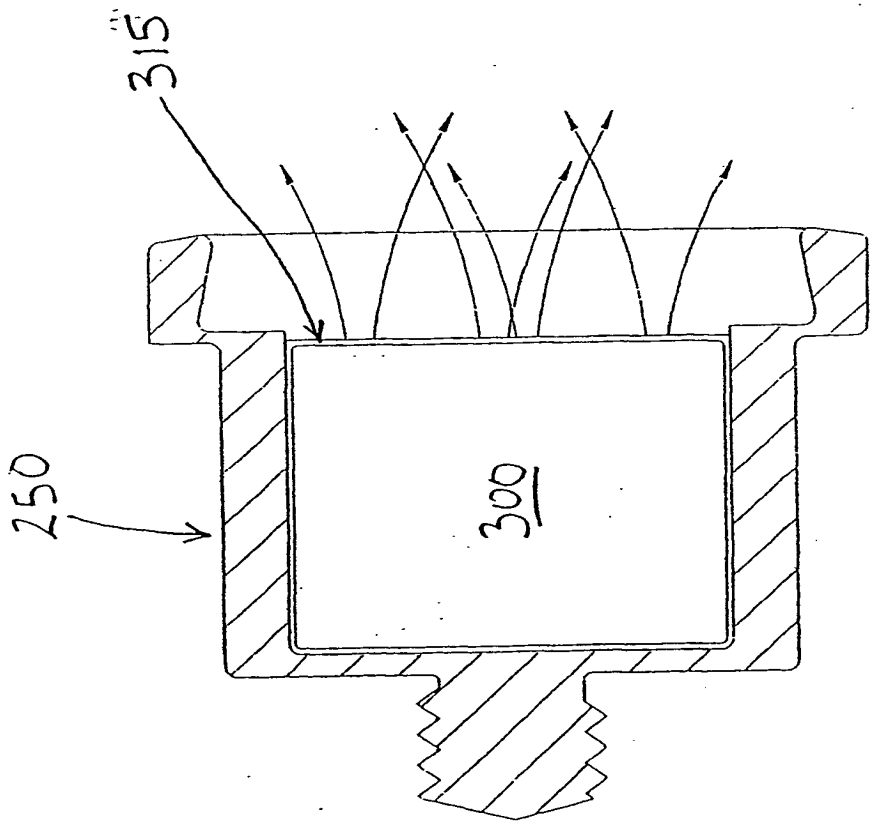
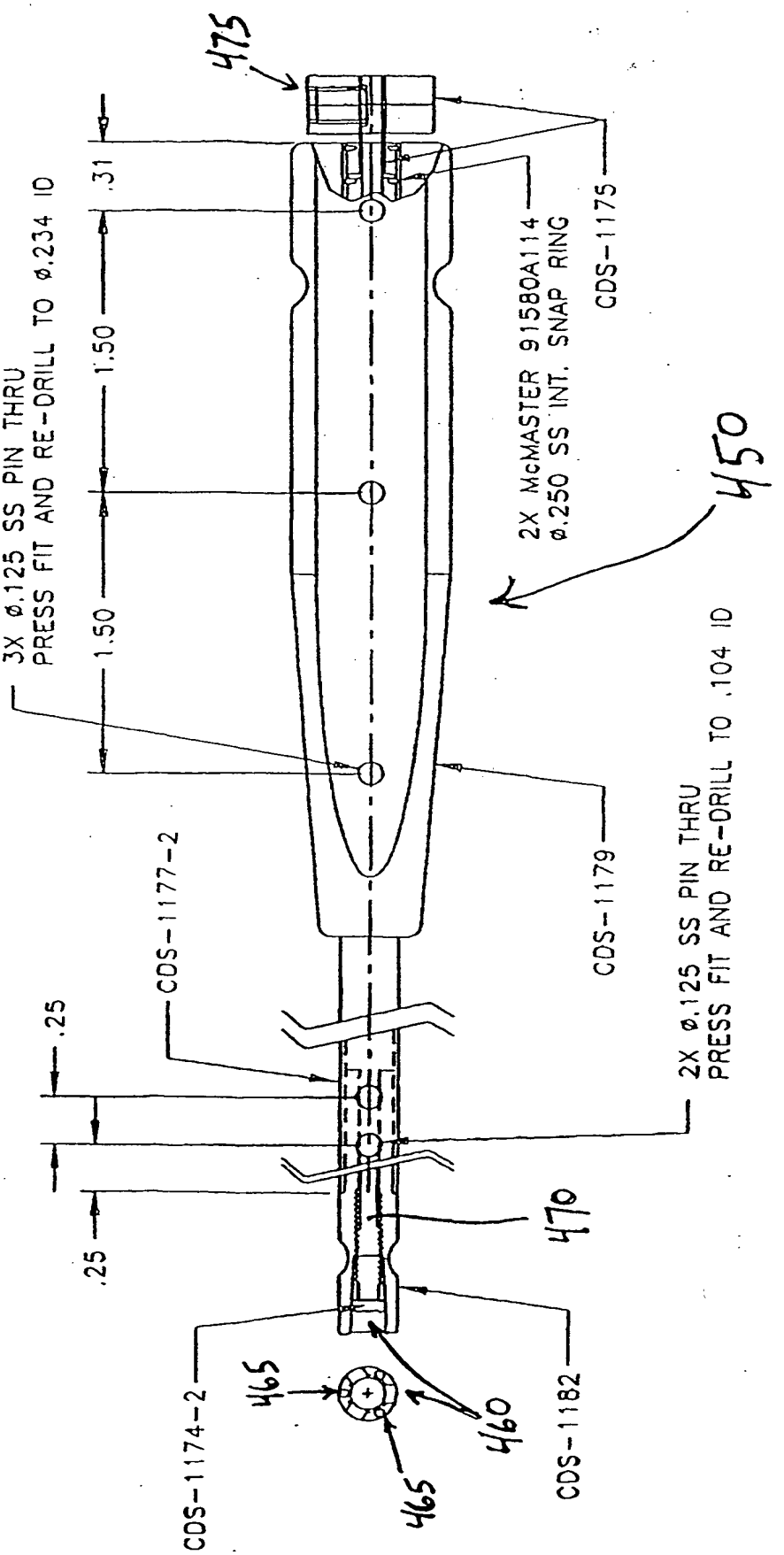


Figure 14D


475
.31
1.50
1.50
3X ø.125 SS PIN THRU
PRESS FIT AND RE-DRILL TO ø.234 ID
2X McMASTER 91580A114
ø.250 SS INT. SNAP RING
CDS-1175
450
CDS-1177-2
CDS-1179
2X ø.125 SS PIN THRU
PRESS FIT AND RE-DRILL TO .104 ID
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.25
470
465
460
465
CDS-1174-2
CDS-1182

Figure 15A

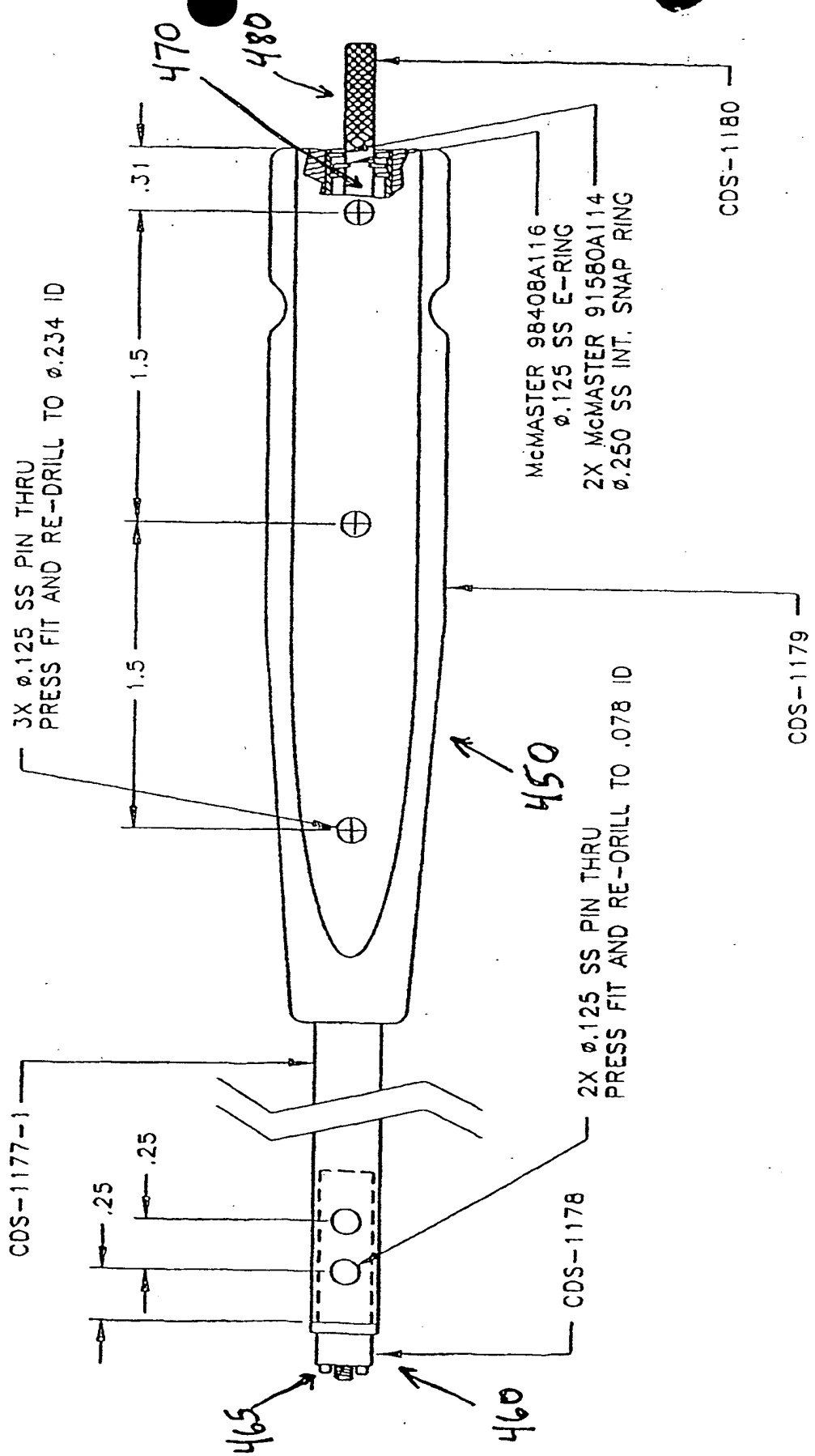


Figure 15B

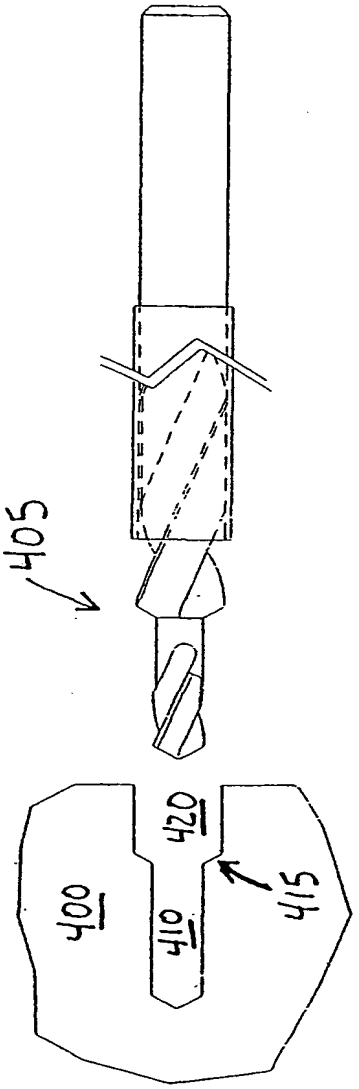


Figure 16A

Figure 16B

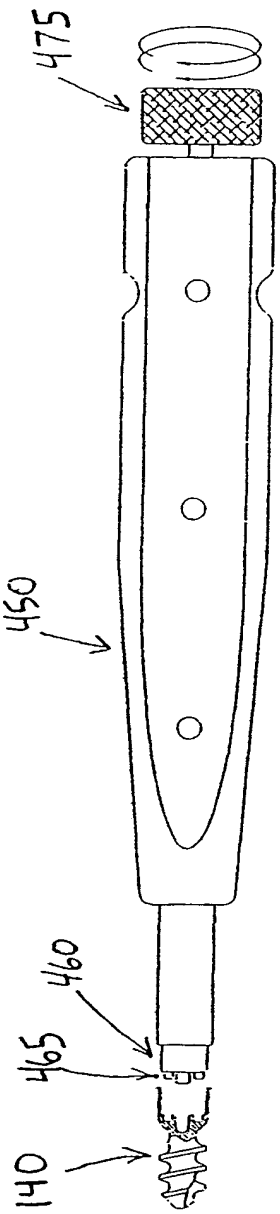


Figure 16C

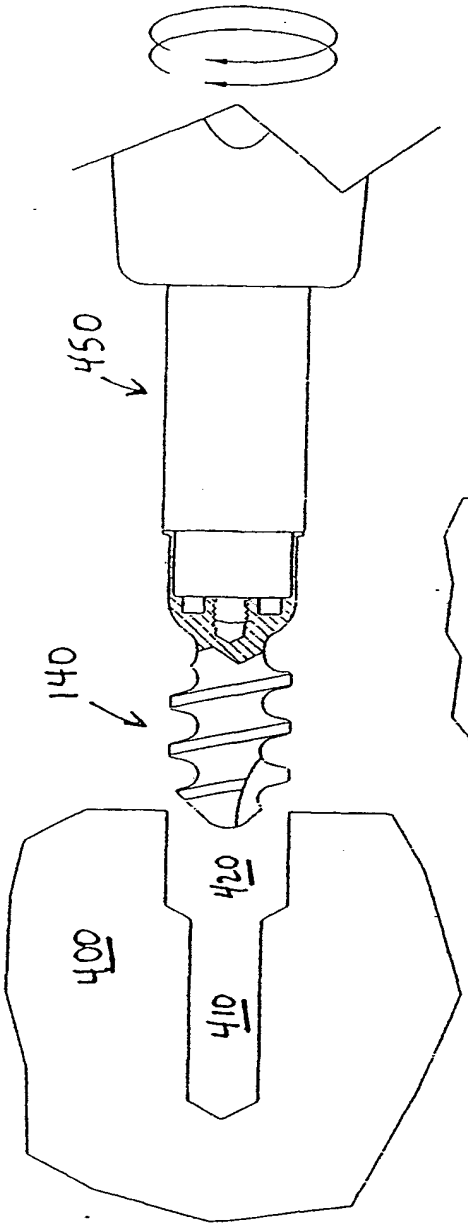


Figure 16D

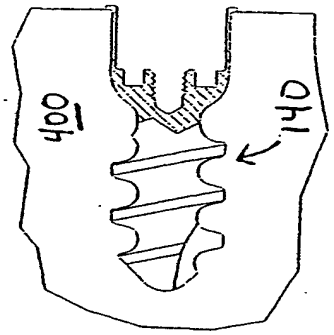


Figure 16E

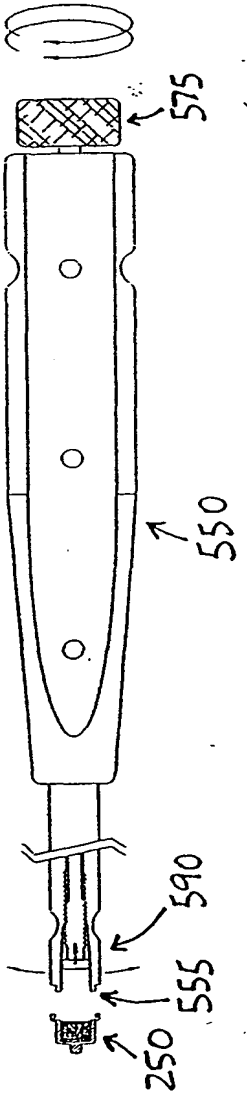


Figure 16F

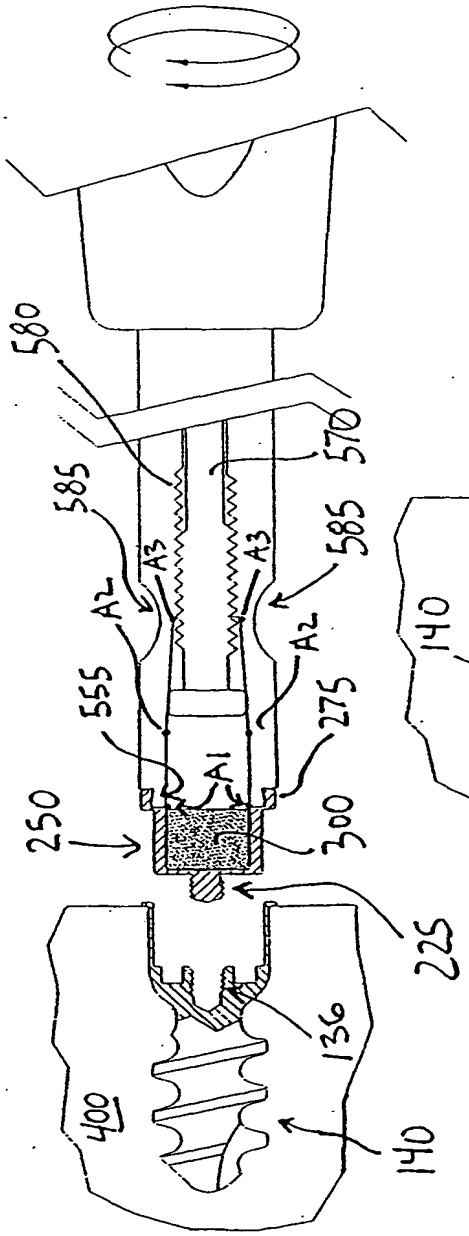
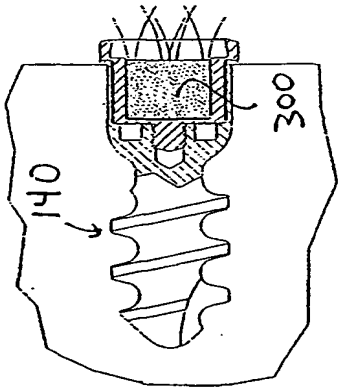


Figure 16G



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60/291,606	18 May 2001 (18.05.2001)	US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

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Published:
— *with international search report*

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10 April 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/036175 A3

(54) Title: SUSTAINED RELEASE DEVICE FOR TREATING CONDITIONS OF THE JOINT

(57) Abstract: An implantable drug delivery system is provided including a mechanical member attachable to a portion of a body, a first chamber having an opening configured to receive a sustained release device, a sustained release device, and a removably attachable retainer for retaining the sustained release device in the first chamber. A method for administering a drug to a joint is provided including the steps of positioning a mechanical member in or adjacent a bone, the mechanical member configured to hold a sustained release drug delivery device at a substantially controlled rate. Also provided is a sustained release device intraarticularly implantable into a joint to deliver a therapeutically effective compound within a synovial capsule of the joint such that, in one aspect, the synovial fluid concentration of the compound is greater than the plasma concentration of the compound during the prolonged lifetime of the device, thereby eliminating unwanted systemic side effects and the need for frequent and repeated administrations.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/42895

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/30 A61M31/00 A61P19/02 A61B17/ A61B17/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EPO-Internal, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 001 386 A (ASHTON PAUL ET AL) 14 December 1999 (1999-12-14) column 5, line 11 -column 6, line 52; claims 17,18	1-9
X	US 5 902 598 A (ASHTON PAUL ET AL) 11 May 1999 (1999-05-11) column 10, line 48 - line 52; claims 14,27 column 11, line 36 - line 45	1-8
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 November 2002	05 DEC 2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Escolar Blasco, P

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,X	BIAS P ET AL: "SUSTAINED-RELEASE DEXAMETHASONE PALMITATE PHARMACOKINETICS AND EFFICACY IN PATIENTS WITH ACTIVATED INFLAMMATORY OSTEOARTHRITIS OF THE KNEE" CLINICAL DRUG INVESTIGATION, ADIS INTERNATIONAL, AUCKLAND, NZ, vol. 6, no. 21, 2001, pages 429-436, XP001080728 ISSN: 1173-2563 abstract	1-3
X	BROWII K ET AL: "A NOVEL CONTROLLED-RELEASE INTRAARTICULAR DELIVERY SYSTEM" ARTHRITIS AND RHEUMATISM, LIPPINCOTT, PHILADELPHIA, US, vol. 9, SUPPL, no. 36, 7 November 1993 (1993-11-07), page S267 XP001080731 ISSN: 0004-3591 abstract	1-3
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ILLI O E ET AL: "Stimulation of fracture healing by local application of humoral factors integrated in biodegradable implants." EUROPEAN JOURNAL OF PEDIATRIC SURGERY: OFFICIAL JOURNAL OF AUSTRIAN ASSOCIATION OF PEDIATRIC SURGERY... 'ET AL! = ZEITSCHRIFT FUR KINDERCHIRURGIE. GERMANY AUG 1998, vol. 8, no. 4, August 1998 (1998-08), pages 251-255, XP009001118 ISSN: 0939-7248 abstract page 254, right-hand column, paragraph 5 -page 255, left-hand column, paragraph 4 ---	11-13, 23-27, 29,30
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X	US 5 192 282 A (DRAENERT KLAUS) 9 March 1993 (1993-03-09) abstract column 3, line 20 - line 55 column 2, line 12 - line 19; example 6 -----	23

INTERNATIONAL SEARCH REPORT

[redacted]ational application No.
PCT/US 01/42895

Box I Observations where certain claims were found unsearchable (Continuation of ite[redacted]f first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

claims 1-10, 29, 30: Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-10

A method of locally administering a therapeutically effective compound to a joint of a mammal by intraarticularly implanting a sustained release device to deliver said compound within the synovial capsule of the joint (in such a way that the synovial fluid concentration of the compound is greater than its concentration in plasma during substantial lifetime of the device).

2. Claims: 11-14

An implantable sustained release device for locally administering a drug, the device comprising a bone screw with a hollow portion (the screw configured to receive a sustained release holding device, which is configured to receive a drug payload).

3. Claims: 15-22

A system comprising:
- a mechanical member attachable to a portion of the body,
- a first chamber with an opening and a removably attachable retainer for retaining a sustained release device,
- a sustained release device.

4. Claims: 23-28

A system comprising:
- a mechanical member attachable to a portion of the body,
- a chamber within the mechanical member (configured to receive a sustained release device bearing at least one drug) having an opening to permit release of the drug borne by the device.

5. Claims: 29-30

A method of administering a drug to a joint by positioning a mechanical member in or adjacent a bone (said member configured to hold a sustained release drug delivery device at a substantially controlled rate) and outputting said drug at a substantially controlled rate.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/42895

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